Signal Detection

The 2005 IOM Safety Framework for Dietary Supplements: Adverse Event Monitoring

The 2005 IOM report suggested that, given the limited resources available to the FDA, a supplement should undergo a safety review only when the signal of a serious adverse event indicates the need. However, should resources permit, it was proposed that the FDA's attention should focus on signals that indicate a serious health problem may result from ingestion of a dietary supplement ingredient.

The 2005 IOM report framework suggested that if the FDA were able to operate proactively, review of a dietary supplement ingredient should be initiated on the basis of either a high prevalence of use in the general population, or a high level of use by a particularly vulnerable population.

As Modified for the Military: Adverse Events and Frequency of Use Monitoring

The military should proactively concern itself not only with dietary supplements associated with an adverse event but also with those most commonly sold on base, and with consideration for the safety of those military personnel who, because of their duties, would be particularly vulnerable to the adverse effects of specific supplements. For example, pilots might be susceptible to effects including hypoxia, cognitive decrements, or loss of spatial orientation. Similarly, those on active duty in adverse environments might be particularly vulnerable to supplements causing loss of thermal regulation (see Chapter 1, Box 1-3 for a list of special military populations). Conversely, if there were supplements that could aid in prevention of these adverse effects, this information might be of considerable benefit to the military.

Initial Review of Signals

The 2005 IOM Safety Framework for Dietary Supplements: Severity of Adverse Events

The second step in the process outlined in the 2005 IOM framework is the initial review of available information on the signal (i.e., adverse event reports). First, the nature of the signal information is examined to determine the preliminary level (low, moderate, or high) of concern about a potential risk to human health. This is not a detailed analysis of data, but rather an assessment to determine whether further evaluation of the supplement is indicated. If review of the reports shows an isolated case lacking reliable evidence that the supplement was likely to be a cause, the resulting low level of concern would indicate no further need for action at that time. If signal review results in even a moderate level of concern traced directly to the supplement, then other criteria, such as prevalence of use or potential to adversely affect vulnerable subpopulations, should be considered, which might result in elevation of the signal concern level to high. Signal review would typically be triggered by an adverse event report of medium or high concern.

As Modified for the Military: Severity of Adverse Events and Frequency of Use

> **Recommendation 4: The decision to initiate a review of a dietary supplement should be based on two criteria: severity and number of adverse events, and prevalence of use. The selection of dietary supplements for review should consider the particular vulnerabilities of the military subpopulations, which would depend on their missions and mission environments.**

Severity and number of adverse events As with the general population, one set of criteria relies on adverse event(s) reported by military or nonmilitary personnel. (See Chapter 6 for recommendations on a system to monitor adverse events for the military.)

Military health care professionals should identify any adverse events associated with dietary supplement use that might compromise the performance or survivability of military personnel. Such adverse events would include those that affect vigilance; have a significant adverse impact on alertness, mood, or cognitive performance; cause hypoxia; or affect balance or spatial orientation. They would also include impairment of clotting, hydration, immune function, or thermoregulation. Conditions to help categorize adverse events as high, moderate, low, and minimal are listed in Box 5-1. Summaries of adverse event reports should be submitted to the military committee or entity designated to oversee dietary supplements (herein referred to as the designated oversight committee; see Chapter 6), who will identify a signal of concern for a dietary supplement and determine whether a review is appropriate.

When the adverse event reported is serious or might compromise performance or survivability, the committee proposes a two-part response. The first step is to determine whether urgent action (e.g., new policies; see Figure 5-1) is warranted. Second, in conjunction with policy implemention and enforcement, a safety and efficacy review should be conducted. Adverse events of moderate concern might not signal the need for new policy, although the military should initiate a safety review (Figure 5-1). If no adverse effects are being noted from the use of a specific supplement and its safety review reveals no concern, then the determination would be made that the dietary supplement is of minimal concern and no further evaluation would be needed. Nevertheless, due to low reporting rates of adverse events,[1] the lack of such reports does not necessarily mean that the dietary supplement is safe. Further, the committee believes that because these products are bioactive, high frequency of use calls for a review of safety, unless the dietary supplement has already been declared to be of minimal concern.

The committee cautions that the linking of an adverse event to a dietary supplement ingredient might be confounded if the product contains multiple ingredients, or adulterants or adventitious contaminants. In the case of multiple ingredients, determination of causation for a particular substance requires careful review of all the individual ingredients in a product or the combination product itself. If contamination is the issue, then attribution of the source of the event is even more challenging. In either case, and until the cause of the adverse event is determined, the military might need to apply policies for the use of the suspect product as well as for any other product containing any of the ingredients found in the suspect product.

Prevalence of use A second criterion to commence a review relies on a proactive initiative by military leadership in response to the use of a new supplement similar to a drug or supplement that has previously caused safety concerns (e.g., bitter orange contains synephrine, closely related to ephedrine, the active component in ephedra); the high frequency of use of a supplement; or an increase in frequency of use in the general military population or specific subpopulations. To make such decisions, data from dietary supplement sales and survey data on dietary supplement use within the military would be required (see Chapter 2). For example, the military should review data on sales of dietary supplements from outlets located on base (e.g., Army and Air Force Exchange Service/Navy Exchange Service [AAFES/NEX], fitness centers) annually to determine which supplements have become popular. Because of the low reporting rates for adverse events, the lack of data on adverse events does not necessarily show that a dietary supplement is safe. Also, because these products are bioactive, a review of the safety of widely used dietary supplements is warranted unless the dietary supplement has been declared to be of minimal concern. If no ad-

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[1] The 2007 Dietary Supplement and Nonprescription Drug Consumer Protection Act defines the term "serious adverse event" as an adverse event that (A) results in (i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity; (v) a congenital anomaly or birth defect; or (B) requires, based on reasonable medical judgment, a medical or surgical intervention to prevent a previously listed outcome described under subparagraph (A).

BOX 5-1
Description of Concern Levels Specific to Use of Dietary Supplements by Military Personnel

High concern

- Human epidemiological studies or adverse effects signaling:
    - Product has been found responsible for a serious adverse event
    - Performance degradation (e.g., for those deployed, in training, or in combat settings):
        - Product significantly affects vigilance
        - Product has significant adverse impact on alertness/drowsiness, mood alteration, cognitive performance
        - Product significantly induces hypoxia
        - Product significantly affects balance and spatial orientation
    - A decrease in survivability (e.g., for those deployed, in training, or in combat settings):
        - Product significantly inhibits clotting time
        - Product significantly promotes dehydration
        - Product significantly inhibits immune system
        - Product significantly disrupts body's ability to maintain thermal regulation
- Animal data signaling:
    - Serious adverse events as described above for human data, seen in animals at doses 10× recommended exposure for humans
    - Neoplasia
    - Severe organ toxicity (necrosis/dysplasia)
    - Reproductive failure/developmental effects
    - Severe neurological/behavioral changes
- In vitro data signaling:
    - Multiple different assays suggest the same pathological condition related to serious adverse events described for human data above
    - Concentrations of the dietary supplement causing severe adverse effects in vitro are similar to reported blood or plasma levels in humans following consumption of this dietary supplement
    - Chemical or plant species is similar to known toxic compound and/or banned dietary supplement, or similar to products having adverse effects described above in humans

verse effects are noted from the use of a specific supplement and its safety review reveals no concern, then the determination would be made that the dietary supplement is of minimal concern and no further evaluation would be needed.

Many factors need to be taken into consideration in determining a level of concern from adverse events reported, including the strength of the

Moderate Concern

- Human epidemiological studies or adverse events signaling:
    - Performance degradation (e.g., for those deployed, in training, or in combat):
        - Product has moderate impact on hydration, gastrointestinal function (e.g., diarrhea, nausea), thermal regulation, alertness/drowsiness, mood, or cognitive performance or may induce shortness of breath or syncope
    - A decrease in survivability (e.g., for those deployed, in training, or in combat):
        - Product has moderate impact on clotting time
        - Product has moderate or low ability to inhibit immune system
- Animal data signaling:
    - Moderate organ toxicity (atrophy, hyperplasia)
    - Reduced reproductive capacity/mild developmental effects
    - Altered clinical chemistry outside the reference range
    - Those adverse effects listed above as serious in humans, occurring at 100× the recommended dose range

Low Concern

- Human epidemiological studies or adverse events signaling:
    - Performance degradation:
        - Product has low impact on hydration, gastrointestinal function (e.g., diarrhea, distress, nausea), alertness/drowsiness, thermal regulation, mood, or cognitive performance
    - No decrease in survivability (product has no known impact on immune response or bleeding/clotting time)
- Animal data signaling:
    - Reduced food intake
    - Enzyme changes
    - Reversible degenerative changes

Minimal Concern

- Human epidemiological studies or adverse events signaling:
    - No serious adverse events
    - No performance degradation (product has no known impact on hydration, gastrointestinal function, thermal regulation, alertness/drowsiness, mood, or cognitive performance)
    - No decrease in survivability (product has no known impact on immune response or bleeding/clotting time)

evidence (e.g., how many adverse events were associated with the dietary supplements, the strength of the association, level of intake, intake of other medications or supplements, actual circumstances of use, characteristics of the individual user). The committee recommended that the evidence be reviewed and that the level of concern be determined by taking into consideration not only the the strength of the evidence but also the tasks

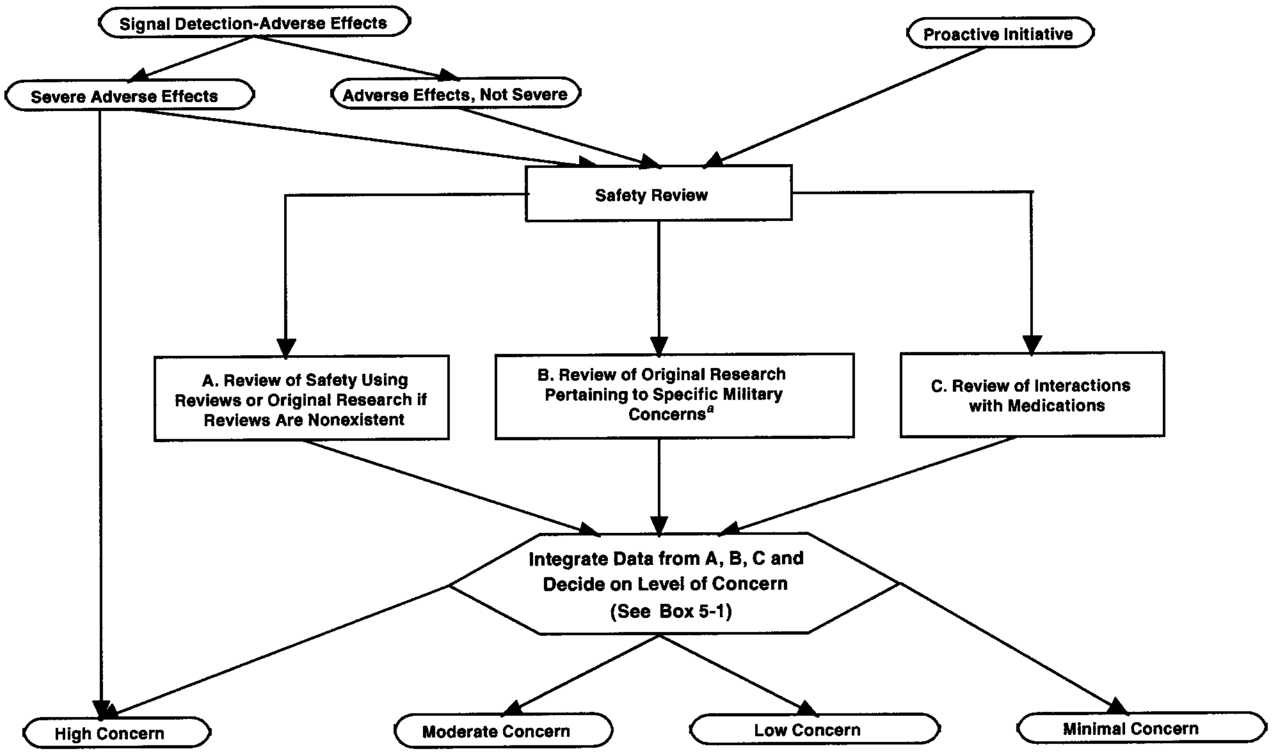
Signal Detection-Adverse Effects
Proactive Initiative
Severe Adverse Effects
Adverse Effects, Not Severe
Safety Review
A. Review of Safety Using Reviews or Original Research if Reviews Are Nonexistent
B. Review of Original Research Pertaining to Specific Military Concerns[a]
C. Review of Interactions with Medications
Integrate Data from A, B, C and Decide on Level of Concern (See Box 5-1)
High Concern
Moderate Concern
Low Concern
Minimal Concern

FIGURE 5-1 Framework to review the safety of dietary supplements.

[a] High physical activity, calorie restriction, hydration, gastrointestinal tract (diarrhea/nausea), liver health/function (xenobiotic clearance), cardiovascular health, mood/behavior altering, alertness/drowsiness, extreme heat/cold, injury/bleeding.

of the specific military subpopulation and the environment in which it will be conducting them (e.g., extreme temperatures or altitudes). As described further in Chapter 6, the designated oversight committee should review adverse events reported by the general population and by the military (as recorded in summaries submitted by the Medical Treatment Facilities' [MTF] Pharmacy and Therapeutics [P&T] Committees), as well as surveys of supplement use by military personnel, on an annual basis. As a result of these examinations, the designated oversight committee might recommend to the military leadership immediate action and/or conducting a review of published, science-based safety reviews by the review panel. The designated oversight committee may call a special meeting or conference call if adverse events are serious or frequent, as judged by the MTF P&T Committees.

Integrated Safety Evaluation

2005 IOM Framework: Integrated Safety Evaluation

The third step of the 2005 IOM report framework is a fully integrated safety evaluation (conducted by a panel of experts) of those dietary supplement ingredients that warrant further investigation based on the concern level raised by initial signal review. There are four components to an integrative evaluation (Figure B-25 in Appendix B): in-depth search and review of literature, drafting of a safety monograph, integrating this information into an analysis to complete the monograph, and review of the draft monograph by an expert advisory committee. In accordance with the FDA's designated function, the 2005 IOM report did not address any potential benefit of a dietary supplement.

Safety reviews of dietary supplements can be performed at various levels, depending on factors such as urgency and the availability of human and economic resources to conduct the review. The 2005 IOM report recommends that four categories of safety data be collected for evaluation following the detection of a signal: human data, animal data, data on related substances, and in vitro data. In conducting the safety review, the panel of experts would also consider possible interactions between a dietary supplement and medications or other xenobiotics. (Examples of monographs and evidence models are available online at http://www.iom.edu/CMS/3788/4605/19578.aspx.) A focused evaluation reviewing only one key ingredient or single area of concern such as cardiac health or renal health might also be appropriate. Both the comprehensive and the focused evaluation might include consultation with an expert committee, FDA personnel, or both, depending on the quality and clarity of the available data.

The integration of the available data using evidence-based principles is the final exercise in establishing a risk level for the dietary supplement, using a causal model diagram that integrates human, animal, in vitro, and even chemical information. Scientific principles for weighting and integrating data from these different categories were described in the 2005 IOM report (see also Jeffery, Box B-14, and Figures B-24 and B-25 in Appendix B).

As Modified for the Military: Integrated Safety Evaluation

> **Recommendation 5: The military should use the framework (Figure 5-1) to review the dietary supplements that raise safety concerns (per criteria above). The framework consists of the integrated evaluation of results from current, authoritative reviews (or, if no reviews are available, original research conducted over the previous 10 years) analyzing bioactivity and potential for drug interactions.**

Efforts to review and summarize information to determine the concern level about a dietary supplement should consider not only individual ad-

BOX 5-2
Approach to Data Collection

The committee developed the following process to characterize the concern level (and efficacy) of a dietary supplement used by military personnel: (1) identify the dietary supplement that warrants review, (2) conduct literature searches, and (3) summarize conclusions about safety (and efficacy).

A proposed search process that is both cost-effective and valuable is summarized in Figure 5-2 as a stepwise decision-making tree. The committee believes that although an evidence-based review of original journal articles might provide a more comprehensive evaluation of safety, an evaluation from well-conducted, authoritative reviews could serve the purpose of alerting the military to potential problems (or benefits) and the need for active management.

In evaluating the safety of dietary supplements, data are needed on two basic attributes: bioactivity (negative or positive) of the ingredients and effects derived from synergistic or antagonistic interactions with other active substances (i.e., in foods, medications, or other active substances).

Bioactivity: Literature searches for systematic reviews of safety and efficacy of the dietary supplement of interest should be carried out in the appropriate databases (primarily PubMed, but also other databases [Napralert, Toxline, SciFinder, or other]). The focus should be on health concerns and unique environmental circumstances of military life. Some areas of particular interest to the military for safety (or efficacy) include specific conditions such as high level of physical activity; restriction of caloric intake; high altitude; extreme heat or cold; health issues such as dehydration, function of gastrointestinal tract, immune, cardiovascular, biliary, or renal systems; and neurobehavioral health. Medical Subject Headings verse events reported but also integrate all other data pertinent to its safety. The scientific principles outlined for the FDA are expected to be used by the military to evaluate the data (see Box B-12 in Appendix B). For the integrated evaluation, the committee recommends an approach less expensive and time-consuming than the full evidence-based review described in the 2005 IOM report: an initial review of safety reviews authored by other reputable scientists (see Box 5-2). Evidence of the effect of interaction of dietary supplements with medications, focusing on medications frequently used by service members, should be taken into consideration. A military review panel should write a monograph for a dietary supplement that raises concerns (see models in Chapters 3 and 4). This review panel will be provided oversight by the U.S. Army Research Institute of Environmental Medicine, an Army medical research laboratory that investigates military nutrition issues. The review panel would include nutritionists, epidemiologists, toxicologists, clinicians, and pharmacognosists. Although contracting performance of the reviews out to a nonmilitary group might be feasible,

(MeSH) terms for the area of interest could help identify key search terms. Original research articles for safety (and efficacy) should be reviewed from the publication date of the last well-conducted review, or for the previous 10 years if no systematic reviews exist.

Interactions with food, medications, or other bioactive substances: Data on interaction with other bioactive compounds are scarce. For identifying interaction with medications, two online databases are particularly recommended: PubMed Plus and Clinical Pharmacology. If the dietary supplement of interest is not included, it may be necessary to search the complete listing of reviews for medication interactions. To enable this, a list should be created of the 100 medications most frequently prescribed for active duty personnel, including mechanism of action and indications for use. This listing should be updated by the military on a regular basis, but initially at least annually. Some of the potential warnings against the use of dietary supplements in combination with medications would be apparent from this list (e.g., the committee cautions against the use of melatonin in combination with other sedative substances). Because of the severe lack of data in the area of interactions, the committee suggests that hypothetical effects from interactions should be based on mechanistic rationale. Likewise, in the absence of clinical data, animal or in vitro data or chemical similarity to ingredients with known interactions can provide suggestive information about potential interactions. Conclusions from these latter approaches are uncertain though, as clinical research data have on occasion refuted initial speculations about synergistic effects. Once information is acquired on a potential interaction, further searches should be done specifically for possible interactive effects of the medication/dietary supplement combination, whether in review articles or original research and using the same databases as above.

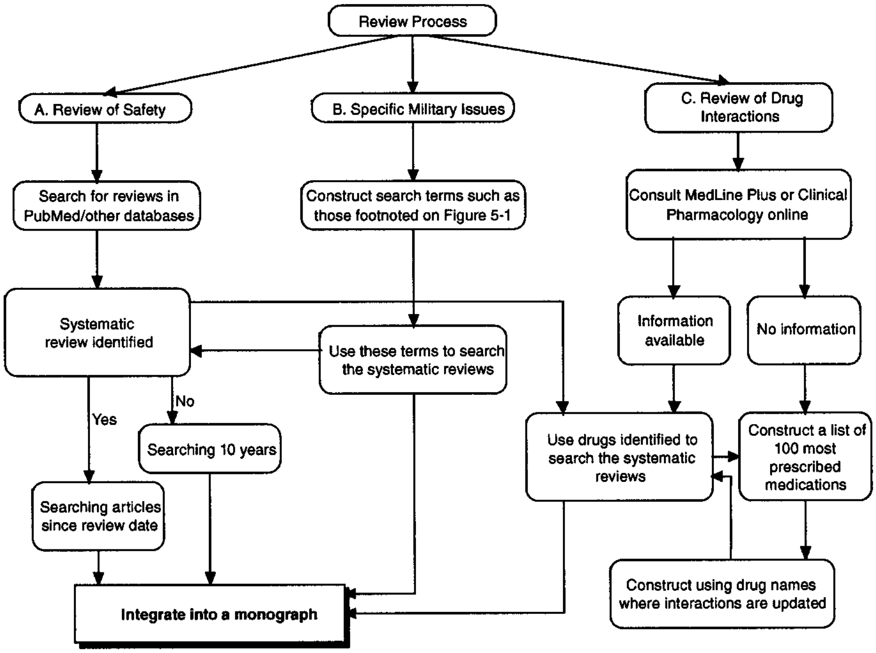
Review Process
A. Review of Safety
B. Specific Military Issues
C. Review of Drug Interactions
Search for reviews in PubMed/other databases
Construct search terms such as those footnoted on Figure 5-1
Consult MedLine Plus or Clinical Pharmacology online
Systematic review identified
Use these terms to search the systematic reviews
Information available
No information
No
Yes
Searching 10 years
Use drugs identified to search the systematic reviews
Construct a list of 100 most prescribed medications
Searching articles since review date
Construct using drug names where interactions are updated
Integrate into a monograph

FIGURE 5-2 Stepwise algorithm depicting search strategy to review the safety of dietary supplements.

the safety and efficacy evaluation as it applies to military situations would be best conducted by a military review panel because they will be more cognizant of the demands and conditions unique to military operations and more experienced in identifying safety concerns relevant to military performance and survivability than a nonmilitary group.

In special cases, this activity could be followed by a more comprehensive safety review of original research, focused on performance and survivability as well as the particular health and environmental situations characteristic of military personnel. Some of these would be related to external situations (e.g., high-intensity physical activity, high altitude, temperature extremes) while some would reflect health concerns for individuals (e.g., injury or bleeding; dehydration; function of the gastrointestinal, immune, renal, hepatic, or cardiovascular system; altered behavior, alertness or drowsiness). This focused approach would not only shorten the length of time necessary for the review, but might also reduce the types of expertise required and ultimately result in information that is more useful. Original research from the time of the last review or, where current reviews are not available, original research conducted over the preceding 10 years, should also be surveyed. As a complement to database searches, a forum or coalition should be established to share data on adverse events and other information on dietary supplements (see Chapter 6).

Once the reviews of the individual dietary supplement are concluded, the review panel should declare its level of concern. The committee developed criteria on which to base the level of concern that use the same principles as the 2005 IOM framework but with a focus on survivability and performance issues (see Box 5-1). The concerns are classified from minimal to high, reflecting the level of performance degradation and survivability and taking into account the special circumstances (environment, hazards, stresses, and performance requirements) of concern to military personnel. If the data are insufficient to establish a level of concern, then the review panel could leave the review incomplete, awaiting further research on safety (and efficacy) or, depending upon the level of military concern, could request that the additional research be performed. It may or may not be appropriate for the military commander to recommend that the substance not be used by military personnel until the determination of concern level has been made.

The committee recognizes that owing to the potential for synergistic or antagonistic effects among ingredients, there are important challenges to applying this framework to products with multiple ingredients. However, because of safety concerns derived from these supplements and ingredient interactions, the committee's approach should also be applied to them. Two approaches to determining level of concern are offered below. In addition, the committee recommends focusing attention on signals from adverse event reporting and data on military usage of these products.

The committee did not provide a framework to evaluate efficacy; however, information on efficacy should also be collected and included in the monograph, since the potential for benefits of a dietary supplement will be factored into the final level of concern.

Decision to Take Action

2005 IOM Framework: A Safety Model for Decision Making

The 2005 IOM report recommends that the results of the safety evaluation should play a pivotal role in the FDA's determination of whether a supplement ingredient is unsafe. Furthermore, because an important component of DSHEA is public education about dietary supplements, it was anticipated that any monograph developed might be made publicly available on the FDA website.

Evidence that results in a high level of concern indicates the need for further investigation to determine whether a "significant or unreasonable risk of disease or injury" (the FDA basis for action) exists. Conversely, the 2005 IOM report suggested that when review of information (either at the initial review stage or as a result of an integrated safety evaluation) indicates a lower level of concern, the FDA should continue to monitor information about the dietary supplement ingredient. Monitoring could consist of passively receiving new signals of concern and/or maintaining routine searches of the scientific literature to gather data about specific existing or new concerns.

As Modified for the Military: Integrating Safety and Efficacy

> **Recommendation 6: The military's decisions on dietary supplement policy (e.g., rules, education, monitoring of use) should be based on conclusions about both safety and efficacy derived from the available published, authoritative scientific literature and considering conditions associated with a specific type of mission, location, and environment.**

Although the development of a detailed process to establish a dietary supplement's level of efficacy was not within the scope of the current task and this committee was not constituted to address the question of efficacy, the committee concluded that considerations of safety and efficacy should be integrated to make decisions about policy on the use of dietary supplements in a military context. A more general description of benefit levels (Table 5-1) was developed by the committee to classify present and future

TABLE 5-1 Guide to Determine Level of Concern and Benefit to Formulate Decisions on Managing Dietary Supplement Use Among Military Personnel, Based on Science and Physiological Effects

Level of Concern or Benefit	Level of Science Documenting an Effect (Concern or Benefit)	Concern or Benefit Specific to Military Mission for Subpopulation of Interest
High	High level of science (large number of consistent high-quality studies)	High concern (or benefit)
Moderate	High level of science (large number of high-quality studies)	Moderate concern (or benefit)
	Moderate level of science	Moderate or high concern (or benefit)
Low/ Minimal/ Uncertain	Any level of science	Low, minimal, or no concern (or benefit)

dietary supplements by potential benefit. The determination of level of benefit is dependent on the number and quality of studies that demonstrate the benefit (or lack thereof) of interest to the military. It is advised that a road map to assess benefits be developed, similar to the framework for safety evaluation.

Because the determination of benefit and concern for a subpopulation is often specific to its mission, location, and environment, decisions on managing the use of dietary supplements should be made by the Office of the Assistant Secretary of Defense (Health Affairs) and by military commanders who will consider these factors along with the scientific evaluation recommended in this chapter. Considerations of the level of concern, potential benefit, and specific military population, tasks, and environments should be integrated in order to decide on appropriate action. The committee has developed the attached matrix (Table 5-2) as a guide to assist the military in making decisions on the use of dietary supplements. The potential actions suggested by the committee can be grouped into three different categories: policy, education, and monitoring. Any decisions for action should be made in consultation with the review panel of experts and the designated oversight committee, who will have a deep understanding of the scientific data.

The framework developed should help the military make decisions regarding the risks and benefits of dietary supplement use by carefully examining the science-based evidence, and should point to research gaps. Making decisions to recommend or restrict the use of a dietary supplement based on the limited data available is difficult. Also, recommendations to use a dietary supplement should be made carefully and only after clear evaluation of risks and benefits, since these recommendations will raise questions related to the personal choice of service members as well as financial and logistical implementation of the recommendation.

The committee recognizes the limitations on making decisions based on balancing risks and benefits; these limitations are related to the availability of data and the evaluation of risks and benefits. For example, for many products, lack of data on safety might preclude the military from determining the concern level. In these cases, the military might decide to support research and restrict the use of the supplement until a concern level can be determined. Furthermore, balancing considerations of benefits and concerns will present difficulties that derive from differences in strength of the evidence for safety and efficacy, lack of suitable indicators to compare the potential benefits and concerns, and the need to weigh the benefits and risks for different subpopulations. Other considerations will also need to enter into the decisions, such as the availability of other methods or supplements to achieve a similar beneficial effect without the risks.

TABLE 5-2 A Guide to Formulating Decisions on Managing Dietary Supplements for Military Personnel, Based on Safety Concerns and Modified by Potential for Benefit

		Suggested Actions Based on Level of Concern/Benefit[a]			
Benefit	Type of Action	High Concern	Moderate Concern	Low Concern	Minimal Concern
High	Policy	2	3	5	6
	Monitoring	7	7	7	7
	Education	8	8	8, 9	8, 9
Moderate	Policy	2	3	—	—
	Monitoring	7	—	—	—
	Education	8, 9	9	9	9
Low	Policy	1	4	—	—
	Monitoring	7	—	—	—
	Education	8, 9	9	9	9

[a] The determination of benefit and concern level for a military subpopulation is often specific to its task, environment, and location. Decisions on managing the use of dietary supplements should be made by the Office of the Secretary of Defense (Health Affairs) and military commanders who will consider these factors along with the scientific evaluation recommended in this chapter.

Policy:

1. DoD, service, and Surgeon General implement policy to prohibit use of product.
2. DoD, service, and Surgeon General specify parameters of use.
3. Unit & MTF commanders make decision on policy based on mission and subpopulation.
4. Posting of warning/educational labels (e.g., at military installation outlets and exercise facilities).
5. Commanders, health care personnel, and fitness center and unit trainers recommend that its use be considered for specific relevant personnel and circumstances.
6. Commanders, health care personnel, and fitness center and unit trainers recommend its use for specific relevant personnel and circumstances.

Monitoring:

7. Monitor for adverse events and frequency of use.

Education:

8. Educate commanders, health care personnel, and fitness center and unit trainers on risks and benefits of specific dietary supplements to enable them to make management decisions.
9. Educate all service members on risks and benefits of dietary supplements in general.

Policy This committee believes that whereas the conclusions about the level of concern and benefit (parallel to the "risk assessment" concept in a risk analysis model) should be determined by scientists (i.e., nutritionists, epidemiologists, and/or toxicologists), the decisions about implementing military policy (paralleling the "risk management" concept in a risk analysis model) should be pursued by commanders at the appropriate level in the military organizational structure. The specific actions taken in response to a dietary supplement review should be the prerogative of military commanders who are knowledgeable about the demands of a particular military subpopulation and its tasks. This model can be successful only when the scientists in the review panel and the designated oversight committee (see Chapter 6) consult and communicate with military leadership and decision makers.

Monitoring Surveillance (generally passive, but also active where there is a high level of concern or high level of potential benefits coupled with low concerns) is a potential management action to assess trends in supplement use, particularly the use of dietary supplements of high concern, multi-ingredient products, or products with high potential for benefit and low concern. Surveys can include questions about the use of any specific dietary supplement of high concern, particularly multi-ingredient products (see Chapter 2). An additional source of information on the use of dietary supplements is on-base (e.g., from AAFES/NEX and fitness centers) sales data. Such data could be gathered on an annual basis for all supplements; such collection is especially advisable for those of high concern level, those containing multiple ingredients, or those with high potential for benefit and low concerns. In addition to providing use trends, data from surveillance are vital to assess the strength of the adverse event signals and serve to complement data from adverse event reports (see Chapter 6).

Education Because members of the military obtain information about dietary supplements from many sources that often have no scientific authority, education based on objective analysis of the efficacy and safety data should be provided on which to make a decision to take supplements not restricted by military policy. Furthermore, educating the commanders, health care providers, and physical trainers about the safety and benefits of dietary supplements of interest or concern will permit these individuals to appropriately exercise leadership and provide guidance to military members. This educational component should be initiated as part of these leaders' formal training and should continue throughout their military careers (see also Chapter 6).

Communication between those responsible for the education of military service members and the designated oversight committee is critical. One way of providing information on dietary supplement safety and efficacy would be to develop a summary table showing both benefits and safety, together with an integrated concern level for the general military population and specific subpopulations (e.g., Table 5-3). Such a table could be used as a basis to develop educational materials for commanders, fitness or

TABLE 5-3 Summary of Risks and Putative Benefits for Selected Dietary Supplements Used by Military Personnel[a]

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Performance enhancers			
Caffeine	Elevation of core body temperature by restriction of peripheral heat loss Elevation of circulating catecholamines at high dosages	Moderate caffeine intake of 400 mg/d has not been associated with adverse effects in most people Mild to moderate locomotor agitation, tachycardia, diuresis, and anxiety. Sleep disturbance can occur if ingestion is within a few hours of sleep time	No data found[i]
Garlic	No data found	Méniere's disease, asthma, bleeding, gastrointestinal disorders	Epidural hematoma, increased international normalized ratio (INR)

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Sympathomimetic stimulant that may have synergy with other psychostimulants An increasing number of dietary supplements, performance-enhancing foods, and sports drinks contain caffeine, even if it is not listed on the label. This can further increase the amount of caffeine being ingested and add to detrimental effects, tolerance, and adverse events	Limited data indicating headache and caffeine craving	Substantial evidence that 100–600 mg caffeine can improve many aspects of cognitive and psychomotor performance during periods of sleep deprivation, and 200–600 mg can enhance physical endurance **High potential for benefit** (substantial evidence of beneficial effects for performance during sleep deprivation)	**Moderate**
Saquinavir: Clinically substantial reduction of AUC Ritonavir: No effect on AUC but increased incidence of gastrointestinal side effects Warfarin: Increased clotting time and INR, additive effect Chlorpropamide: Increased hypoglycemic effect Acetaminophen: Altered metabolism but not clinically substantial	No data found	No clinical studies for mental or physical performance Evidence of antimicrobial effects **Low potential for benefit** (substantial evidence of minimal beneficial effects)	**High** due to potential impact of chronic use on blood clotting

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Ginkgo biloba	No data found	Transient headaches, gastrointestinal disturbances, sleep disturbances, bleeding with Warfarin and aspirin	No data found
Ginseng	No data found	Gastrointestinal effects	No data found
Tyrosine	No data found	No data found	No data found
Quercetin	No data found	No data found	No data found

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Warfarin, NSAID, alcohol: Theoretical interactions but studies do not support interactions Omeprazole: Reduced plasma concentrations of dietary supplement Thiazide diuretics: Reduced efficacy of diuretic	No data found	Little evidence of cognitive benefits in healthy, young individuals **Low potential for benefit** (substantial evidence of minimal beneficial effects)	**High** due to potential impact of chronic use on blood clotting
Warfarin: Three case reports reporting reduction in the INR Phenelzine: Induced mania Influenza vaccine: Increased the efficacy of vaccine when given in combination Alcohol: Reduced blood alcohol concentration	No data found	No benefits to physical performance in healthy, young individuals Some evidence of memory improvement and reduction in mental fatigue **Low potential for benefit** (substantial evidence of minimal beneficial effects)	Low
Theoretical with monoamine oxidase inhibitors	No data found	Evidence of improvement of cognitive function, mood states, and psychomotor functions especially under stressful situations **Moderate potential for benefit** (moderate level of science but high desirability)	**Minimal**
No data found	No data found	Some evidence of immune system improvement and antiviral properties **Moderate potential for benefit** (some level of science but high desirability)	**Minimal**

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Anabolic supplements (reported as "bodybuilding supplements" in surveys)			
Steroids			
Dehydroepiandrosterone (DHEA)	No data found		Neoplasia in rat studies, correlation to breast cancer in epidemiological studies, androgenizing effects in women
Nonsteroids			
Beta-hydroxy-beta-methylbutyrate	No data found	No data found	No data found

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Some drugs decrease DHEA blood levels (ACTH inhibitors and P450 inducers); caution when used concurrently with hormonal therapies	No data found	No effect on body composition, muscle, or cognitive function Some evidence for improvement in bone health and mood in older women **Low potential for benefit** (some evidence of minimal beneficial effects)	**High**
No data found	No data found	Some evidence of increase in lean tissue and muscle strength of untrained individuals **Moderate potential for benefit for untrained individuals or those in catabolic states such as negative energy balance** (moderate level of science but high desirability)	**Minimal**

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Creatine	Consider possibility of dehydration or renal effects	Case reports of renal failure No dehydration or gastrointestinal problems	No data found
Weight loss			
Ephedra (Ma huang)	No data found	Case reports of psychosis, vision impairment, muscle failure	Two- to fourfold increase in adverse effects: increased blood pressure, palpitations, heart rate. Case reports of cardiovascular adverse effects, stroke, psychosis, heart failure, seizure, vision impairment, transient ischemic attacks, muscle failure, and death
Chromium picolinate	No data found	Only isolated adverse effects reported (changes in cognitive behavior, allergic skin disorders, renal failure, and liver dysfunction)	Only isolated adverse effects reported

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Caffeine: Synergistic effect and opposing effects reported NSAID and some vitamins: Theoretical interactions	No data found	Substantial evidence of improvement in physical performance Substantial evidence of increase in muscle mass Some evidence of improvement in cognitive and psychomotor performance Potential for protection against traumatic brain injury **Moderate potential for benefit** (moderate evidence of benefits and high desirability)	Low
Interactions with other sympathomimetic drugs such as caffeine	Palpitations	Few studies show a small but substantial effect for weight loss Clinical studies show no evidence for performance enhancement **Moderate potential for benefit** (for weigh loss) (moderate level of science but high desirability)	**High**
Absorption reduced with phytates and medications that alter acidity of stomach	No data found	Some evidence of small effects on weight loss and body composition **Low potential for benefit** (substantial evidence of minimal beneficial effects)	Low

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Sleep aids			
Melatonin	Drowsiness/ sedation effects	Loss of core body heat Drowsiness/ sedation effects Gastrointestinal effects	No data found
Valerian	Drowsiness/ sedation effects	Drowsiness/ sedation effects Gastrointestinal effects	No data found
General health[j]			
Energy supplements[k]			
Sports bars	No data found	No data found	Could contribute to superfluous calories for inactive personnel

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Sedative hypnotics and anesthetics: Theoretical synergy	No data found	Some evidence of improvement of sleep Substantial evidence of circadian reentrainment under controlled conditions **Moderate potential for benefit** (evidence of circadian benefits and some sleep benefits)	**Moderate**
Sedative hypnotics and anesthetics: Theoretical synergy	No data found	Inconclusive evidence that valerian improves sleep **Low potential for benefit** (evidence of minimal beneficial effects)	**Moderate**
Unknown but unlikely, depending on individual ingredients	No data found	Evidence of improved exercise performance Supplement essential nutrients **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal**

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Sports drinks	No data found	Hyponatremia (with excessive use)	Could contribute unnecessary calories for inactive personnel
Vitamins and Minerals			
Calcium	No data found	Minimal when below Tolerable Upper Intake Level (UL)	Minimal when below UL

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
Unknown but unlikely, depending on individual ingredients	No data found	Evidence of improved exercise performance Some evidence of increased muscle protein synthesis, superior hydration, and reduction in muscle damage after strenuous exercise when drinks contain protein; requires further substantiation Plasma level better maintained during sweating when electrolytes are provided **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal**
May reduce absorption and/ or efficacy of some medications	No data found	To reach adequate levels by supplementing the diet Sustain bone health and mood states; potential for further benefits with supplemental amounts **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal** when below UL

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Iron	No data found	Minimal when below UL	Minimal when below UL
Selenium	No data found	Minimal when below UL	Minimal when below UL
Zinc	No data found	Minimal when below UL	Minimal when below UL
Multivitamins/ multiminerals	No data found	Minimal when below UL	Minimal when below UL

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
	No data found	To reach adequate levels by supplementing the diet Sustain physical and cognitive performance **High potential for benefits** (substantial evidence of benefits and high desirability)	**Minimal** when below UL
	No data found	To reach adequate levels by supplementing the diet Maintain immune function; potential for further benefits with supplemental amounts **High potential for benefits** (substantial evidence of benefits and high desirability)	**Minimal** when below UL
	No data found	To reach adequate levels by supplementing the diet **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal** when below UL
	No data found	To reach adequate levels by supplementing the diet **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal** when below UL

continued

TABLE 5-3 Continued

	Potential Detrimental Effects to		
Dietary Supplements[b]	Military Performance[c]	Military Survivability[d]	Other Health Risks[e]
Vitamin C	No data found	Minimal when below UL	Minimal when below UL
Vitamin D	No data found	Minimal when below UL	Minimal when below UL
Vitamin E	No data found	Minimal when below UL	Minimal when below UL

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[a] The monographs used to produce this table were developed in order to evaluate the review process outlined in Chapter 5. The monographs present scientific reviews of safety and efficacy, but do not attempt to provide a final assessment of safety or efficacy.

[b] Composition of dietary supplements varies widely; these are general categories and many include other ingredients or a combination of ingredients.

[c] Causing detriments to performance during military tasks (e.g., physical endurance, muscle strength, alertness, memory, stress, sleep patterns).

[d] Causing detriments to military survivability (e.g., bleeding or injury, dehydration, malfunction of gastrointestinal tract, stress, or altered behavior).

[e] Causing risks to health, excluding those in note 2 above.

[f] Refers to the 100 medications most prescribed for military personnel.

[g] Improvements of performance during military tasks (e.g., physical endurance, muscle strength, alertness, memory, stress relief, sleep patterns) based on level of desirability of the benefit to the military and level of science documenting a benefit (see details in Table 5-2).

[h] High, moderate, low, or minimal as described in Box 5-1 and modified based on putative benefits.

Interactions with Medications[f] or Other Bioactive Substances	Withdrawal Effects	Putative Benefits[g]	Concern Level[h]
	No data found	To reach adequate levels by supplementing the diet Maintain immune function **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal** when below UL
	No data found	To reach adequate levels by supplementing the diet Maintain bone health **High potential for benefits** (substantial evidence of benefits and high desirability)	**Minimal** when below UL
Aspirin: Antithrombotic effects Warfarin	Unknown but unlikely	To reach adequate levels by supplementing the diet Maintain immune function **High potential for benefit** (substantial evidence of benefits and high desirability)	**Minimal** when below UL

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[i] "No data found" means that there were no data found in the subject area showing an effect, either because the studies reviewed did not investigate this subject area or because, when investigated, there was no effect (i.e., health risk). Absence of evidence of risk, a frequent reality, does not necessarily indicate that there is no risk. Even if a study reported a lack of adverse effects, if the study is not adequately designed to identify risk (e.g., it is insufficiently powered, incompletely reported, does not include positive controls, or otherwise has inadequate mechanisms for detecting adverse events), its scientific validity is reduced or even null.

[j] Immune function enhancers, antioxidants, energy supplements, enhance recovery or performance.

[k] Refers to supplements containing macronutrients for energy or essential nutrients below the UL to meet physiological needs level, or electrolytes to replenish those lost during exercise. If energy supplements contain other ingredients (e.g., creatine), then an evaluation of each individual ingredient and interaction is warranted.

military unit trainers, and health care providers to inform service members. The committee cautions that such a summary table could be misinterpreted and therefore is not to be used as a sole source of information; it is meant to be used by those with sufficient scientific expertise as a tool to develop educational materials. Communication with service members should not establish a presumption that using dietary supplements is the norm or the expected behavior.

CHALLENGES OF THE PROPOSED FRAMEWORK FOR MILITARY PERSONNEL

The three types of challenges in evaluating the safety or efficacy of dietary supplements with the framework proposed by this committee are outlined in this section.

Insufficient Scientific Data

The practical value of the proposed framework depends on publicly available data. One critical challenge is acquisition of sufficient scientific data from literature searches to support an informed decision about the safety and efficacy of a dietary supplement within the military. Although there is an abundance of data for a few supplements, such as ephedra, the dearth of data for others hinders the determination of any definitive conclusion and further decision making. In Chapter 7, the committee provides its recommendations on the military undertaking research to address data gaps in areas of significant concern.

The committee emphasizes that absence of evidence of risk, a frequent reality, does not necessarily indicate that there is no risk. Even if a study reported a lack of adverse effects, if the study is not adequately designed to identify risk (e.g., it is insufficiently powered, incompletely reported, does not include positive controls, or otherwise has inadequate mechanisms for detecting adverse events), its scientific validity is reduced or even null.

Multi-Ingredient Dietary Supplements

Dietary supplements commonly contain multiple ingredients, and their compositions are frequently altered (e.g., they are reformulated with different proportions, amounts, and even ingredients) without any product name change. Finding data on the safety (or efficacy) of the myriad multi-ingredient products in the market is yet a bigger challenge than finding data on single-ingredient products. The committee concluded that these products merit special attention by frequent monitoring of their use, sales, and adverse event reports. The following are two potential approaches to determining the safety (or efficacy) of these products. Recognizing that both of these approaches (i.e., determining the safety of a total product or determining the safety of individual ingredients) have advantages and disadvantages, the application of either approach to evaluate the safety (and efficacy) of multi-ingredient products should be the prerogative of the military. Among other factors, the military should consider the strength of detected signals, prioritization of research gaps, and availability of resources. For either approach, there will be additional staff support required to maintain continuous surveillance of multi-ingredient products, including all the possible interactions.

Determining total product safety Given the virtual absence of data on multi-ingredient products, the military could decide to conduct research with study designs addressing military subpopulations and environments of interest, an approach that would be both expensive and time-consuming. In addition, the rapid turnover of products in the market may make it difficult or impractical to keep such research current.

Determining ingredient safety The level of concern (or efficacy) associated with the consumption of a multi-ingredient product could be determined by examination of each individual ingredient and of each potential interaction using the approach recommended in this chapter. The challenges in this case relate not only to the ingredients themselves but to the potential interactions among ingredients in the product. Furthermore, safety data on ingredient interactions are typically unavailable.

Presence of Contaminants

The linking of an adverse event to the use of a dietary supplement ingredient might be confounded if the product contains adulterants or contaminants. Attribution of the source of the adverse event becomes a formidable task. If enforced, the newly adopted cGMP rule should minimize the potential for inclusion of adulterants or contaminants. Because this rule will not be implemented until June 2008, its effectiveness remains to be evaluated.

OVERALL RECOMMENDATIONS

The committee recommends that the military use the proposed framework, modified from the 2005 IOM report framework, to determine whether a dietary supplement requires that military leadership take specific management actions to ensure optimal readiness and health protection of military personnel. This framework provides a methodology with a preestablished search strategy for generating a safety monograph for a dietary supplement, and a consistent format that provides key information which can be used to assist military policy makers. It also provides criteria to initiate safety reviews based on signals generated from an adverse event; or proactively, based on significant changes in dietary supplement consumption by military personnel. The following are overall recommendations related to the application of the framework:

- Determination of the level of concern for a dietary supplement should be based on published reviews of general safety concerns and on adverse effects and/or benefits specific to the military; the final integrated concern level should be predicated on safety concerns, modified by potential benefits, and based on special mission requirements and environments.
- The final, integrated concern level and the need for dietary supplement management should be determined in the context of specific subpopulations of the military and based on their special mission requirements, environments, and locations. This analysis should pay particular attention to military subgroups of interest for whom benefits and safety are of operational concern.
- Dietary supplement management should be predicated on safety concerns, modified by any proven benefits.
- A future task force or committee should more fully describe the process and framework to characterize the efficacy of dietary supplements of interest to the military and describe a detailed process to monitor the emergence of dietary supplements that could provide benefits to the military.
- To determine whether the level of concern for a dietary supplement should be reclassified as future research unfolds, research should be monitored on an annual basis, especially for those supplements for which a concern level could not be established due to lack of data. Based on recommendations of the designated oversight committee, the military might also decide to support or conduct research on a specific dietary supplement depending on its relevance to the military. For example, dietary supplements of military interest that are classified as being of high concern based on equivocal animal data could be referred to the research community to more fully characterize the level of concern in humans. It may or may not be appropriate for the military commander to recommend that the dietary supplement not be used by military personnel until that determination has been made.

REFERENCE

IOM (Institute of Medicine). 2005. *Dietary supplements: A framework for evaluating safety.* Washington, DC: The National Academies Press.

6

Monitoring Adverse Health Effects Associated with Dietary Supplement Use by Military Personnel

BACKGROUND

Making definitive declarations about the safety of drugs, foods, or dietary supplements is a challenging task, even with the most robust premarket studies. Among the multiple strategies (pre- and postmarketing) available, postmarket monitoring of adverse effects associated with these products becomes a very important tool to assess their safety. Often, a postmarket monitoring system serves as a complement to a risk or safety assessment to identify adverse effects that are not recognized in a laboratory or a small clinical study. In the case of food ingredients (i.e., additives and generally recognized as safe [GRAS] substances), the standard of safety is a "reasonable certainty of no harm" as indicated by either the food additive petition approval, GRAS notification, or GRAS self-affirmation process. For example, prior to marketing food additives, a petition that includes a safety assessment (i.e., available data on safety of the product) is sent to the U.S. Food and Drug Administration (FDA). Upon review of the petition, the FDA may issue a safety declaration. Once on the market, there is no established system to monitor adverse events from foods; however, if a new ingredient is introduced to a previously available food product, the FDA might informally ask the manufacturer to conduct postmarket monitoring of adverse events. Receipt of a sufficient number of complaints from consumers or consumer organizations might also prompt the FDA to investigate the safety of an ingredient.

In contrast, for drugs, a premarket risk-benefit analysis is conducted, followed by a postmarket safety evaluation that includes a passive, voluntary surveillance system. The premarket risk-benefit analysis is composed of three types of studies: animal toxicology and pharmacological studies, proof-of-principle studies for the disease or condition being addressed, and confirmatory studies of safety and efficacy (FDA, 2007). As a result of this required risk-benefit review, by the time a medication is on the market there are multiple well-conducted studies available that can later be used in support of an alleged association with an adverse event. Under the Federal Food, Drug, and Cosmetic Act, as amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994, the law that regulates dietary supplement safety, the FDA does not have the authority to require a premarket safety assessment, yet bears the burden of proof to determine that a dietary supplement is unsafe before or after introduction in the marketplace. Because there are no premarket assessments required for dietary supplements, there is a paucity of laboratory safety studies; hence, postmarket monitoring of adverse events becomes even more significant for ensuring public health. DSHEA provided the FDA with the authority to develop monitoring systems and to take necessary actions when it has sufficient evidence that a product is unsafe (*Dietary Supplement Health and Education Act of 1994*, Public Law 103-417, 108 Stat 4325, 103rd Congress, October 25, 1994). The FDA has established a program called MedWatch to provide and elicit information on safety issues; reports from either health care professionals or consumers can be submitted voluntarily to the FDA or manufacturers via a standard form, form FDA 3500 (see Appendix E). The Dietary Supplement and Nonprescription Drug Consumer Protection Act made the reporting of life-threatening events to the FDA by manufacturers mandatory after December 2007 (the MedWatch 3500A form is used for this purpose) (*Dietary Supplement and Nonprescription Drug Consumer Protection Act*, Public Law 109-462, 109th Congress, December 22, 2006). Reports from both consumers and manufacturers are submitted through a passive monitoring system, that is, the FDA does not actively seek the adverse event reports. There are four steps to follow in such a system: (1) detect adverse events, (2) generate signals of public health concerns, (3) assess signals, and (4) take appropriate action.

As with medications and food ingredients, health risks from dietary supplement use are derived mainly from a consumer's individual susceptibility, or from the dietary supplement's inherent biological activity or interactions with medications. For the majority of dietary supplements, inherent toxicity might be expected to be less than that of medications because of the lower concentrations and potency per unit. Nevertheless, there are factors (i.e., the lack of composition standardization or a product compendium, multi-ingredient products, biased consumer attitudes, and a potential of overuse by some consumers) that increase the risks to health from the use of dietary supplements. Because dietary supplements are regulated as foods and many have a history of traditional use, there is a perception that they are safe and do not need a premarket approval process. However, it should be noted that products with a history of safe use may now be used in a different manner (e.g., with different solvents used for extraction, alternative plant parts used, longer duration of use) from traditional uses. Many consumers are also unaware that there is no requirement for federal approval of dietary supplements or advertisements promoting them, mistakenly assuming that dietary supplements must conform to the same regulations as drugs (Ashar et al., 2008). The differences in perception of risk between dietary supplements and drugs should be considered when attempting to model a surveillance system for dietary supplements.

There are many activities critical to the evaluation of risk-benefit profiles, such as adverse event surveillance, confirmatory laboratory safety studies, and data on use. Data from adverse event monitoring are complementary to data on use from dietary supplement surveys: survey data typically focus on the use of a specific dietary supplement within the population, whereas monitoring collects the numbers and types of adverse events resulting from its use. Both estimates are critical when making decisions about the safety of a product because their ratio (i.e., reporting proportion) may provide a rough estimate of the magnitude of a problem; in the case of dietary supplements, low reporting of adverse events and scarce information on dietary supplement use limit the utility of these data. Also, an association of use with an adverse event does not imply the demonstration of causality; rather, it intends to alert decision makers of potential concerns possibly requiring corrective actions. Determining causation requires rigorous clinical trials or research designs performed with animal models, not just analysis of adverse-event report data (IOM, 2005). Associations identified from adverse-event monitoring must be viewed as hypotheses regarding possible causal relationships between the substance and event, recognizing that there may be many possible reasons other than a direct causal relationship for the observed association (Almenoff et al., 2005).

Based on the heightened risks and the absence of an internal military process to report adverse events, this chapter discusses the need for the military to add dietary supplements to its current adverse-event monitoring system for medications so that this system responds to the unique risks and demands of military service. The chapter reviews the adverse-event monitoring efforts for the general population and for the military population, highlights challenges, and recommends improvements that build upon the current military system. Challenges might be categorized as related to the process of adverse event monitoring itself or related to the analysis of the data. Since those relating to data analysis (e.g., data mining statistical methods, identification of trends) are not unique to the military system, the committee discussed them briefly and refers to the published literature for further reading. The committee focused its deliberations on process-related challenges (e.g., low reporting rate; quality of data; use of integrated, electronic data). Taking the current system and policies as its foundation, this chapter makes recommendations for a collaborative approach in which appropriate institutions share data and lessons learned from their respective monitoring systems. The proposed approach will alert the military of potential concerns derived from using specific dietary supplements, particularly when performance might be compromised, and will serve as a signal to initiate appropriate actions by military leadership, as described in Chapter 5.

THE FDA'S PROCESS TO MONITOR ADVERSE EVENTS FROM DIETARY SUPPLEMENTS

To make recommendations about approaches to monitoring military personnel for adverse health events that might indicate a concern associated with consumption of dietary supplements, the committee reviewed the FDA's systems for both medications and dietary supplements. A more detailed description of the monitoring system for products regulated by the FDA is included in Appendix B (see sections by Dal Pan and Frankos and Mozersky). As mentioned above, to gauge the safety of dietary supplements, the FDA relies in part on evaluation of reports of adverse events possibly associated with their use. The FDA uses these evaluations to analyze trends and to detect a signal (i.e., a strong relationship between a dietary supplement and adverse events). However, a determination that a dietary supplement or dietary ingredient is unsafe would be based on a thorough assessment of not just reports of adverse events, but also of the scientific peer-reviewed literature on the safety of the dietary supplement or dietary ingredient.

Adverse events are most often reported via the submission of FDA's MedWatch 3500 form (see Appendix E), which is used to provide information from clinical trials, health care personnel, and consumer reports. To summarize the process, an individual (health care provider or consumer) communicates a description of the event and the patient to the FDA's Center for Drug Evaluation and Research, where the source of the event is categorized by origin (i.e., drug, dietary supplement, devices, biologics). The initial submission might be electronic or via telephone, standard mail, or fax; all reports are transcribed, regardless of the reporting mechanism. Reports are often submitted over the phone by a health care provider and received and transcribed verbatim by an FDA officer who typically does not probe for more information or details about the adverse event. By contrast, some manufacturers hire interviewers or facilitators trained to ask relevant questions of those submitting information on adverse events for entry in the

MedWatch form to be sent to the FDA. When potentially associated with a dietary supplement, reports are redirected to the FDA's Center for Food Safety and Applied Nutrition for evaluation.

For processing, MedWatch 3500 forms require only an identifiable reporter, a patient (anonymized), the suspect product, and a description of the adverse event. The information is reported regardless of the quality of the data, which is not validated. Apart from the patient's personal data and medical conditions, the form includes fields for entry of important information about the product (type, brand name, lot number, expiration date) and use (dose, frequency, date of initiation of use, consistent or inconsistent use, reason for use, last time of use before adverse event). Critical in identifying a signal is the section of the form referring to the event itself: event description, actions taken in response to event (e.g., sought medical attention), and documented diagnosis. FDA officials consider it advantageous to format this section as open-ended questions, offering the possibility of acquiring valuable information about the event circumstances (personal communication, Vasilios Frankos, Center for Food Safety and Applied Nutrition, May 30, 2007). The concomitant use of a drug and a dietary supplement or of a combination of dietary supplements might cause synergistic or antagonistic effects; the section in the form addressing the use of other medications and supplements is also therefore critical in evaluating the signal.

Once information is collected and distributed to the FDA's safety officers, analysis and signal detection follow. If an event is serious or uncommon, further steps are expeditiously taken: (1) a follow-up is requested, (2) other federal agencies are consulted, (3) a review of the literature is initiated, and (4) prior FDA reports on adverse events from similar products are consulted to identify trends. There is, however, no automatic signaling mechanism, and the weight of the evidence is considered case by case; the experience and consensus of safety officers usually dictate the decisions taken.

Until recently, these voluntary submissions and resultant MedWatch 3500 forms provided the only system to obtain information on postmarket adverse events associated with dietary supplements. To strengthen this system, the Dietary Supplement and Nonprescription Drug Consumer Protection Act mandates that after December 2007, serious adverse events[1] voluntarily reported to dietary supplement manufacturers by consumers and others must be submitted by the manufacturer to the FDA via the MedWatch 3500A form (see Appendix D). The form is slightly different from

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[1] The 2007 Dietary Supplement and Nonprescription Drug Consumer Protection Act defines the term "serious adverse event" as an adverse event that (A) results in (i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity; (v) a congenital anomaly or birth defect; or (B) requires, based on reasonable medical judgment, a medical or surgical intervention to prevent a previously listed outcome described under subparagraph (A).

MedWatch 3500 in that it also solicits composition information from the product label as well as the manufacturer's contact information. Although this is a clear enhancement of the dietary supplement regulatory system and there is an expectation that the amount of data collected on adverse events will improve in both quality and quantity, the actual benefits from the act are still to be realized.

The potential misinterpretation of reports has resulted in some reluctance to make adverse event monitoring data available to others (see Kingston in Appendix B). Given the low reporting rate for dietary supplement-related adverse events, and the absence of a well-established system to monitor adverse events, it seems essential for organizations and manufacturers to collaborate to understand the limitations and uses of the current systems for reporting adverse events associated with dietary supplements. For example, the 2007 Institute of Medicine (IOM) report *The Future of Drug Safety* emphasized the importance of partnerships and the need for a concerted effort to make effective use of both public and private resources to address drug safety (IOM, 2007). Efforts to incorporate information from other sources, such as poison control centers (PCCs), have not, for various reasons, always been successful. The PCCs are private organizations whose purpose is to provide medical advice on how to treat an adverse outcome, not to assess the safety of substances. Calls received by PCCs include those prompted by nontoxic or unintended exposures to dietary supplements, medications, or other substances by children. Direct comparison of data from PCCs and MedWatch forms is not appropriate, since the same adverse-event data elements are not collected. The FDA therefore reviews PCC reports only when follow-up is necessary. The FDA has also been working with the University of California at San Francisco to monitor the PCC reports received by the San Francisco Center for Drugs and Dietary Supplements. Through this collaboration, it was determined that most adverse events in the PCC reports that were linked to dietary supplement use were associated with the use of stimulants (caffeine, ephedra-like products) and multi-ingredient dietary supplements, especially weight-loss products, and that these events were often associated with cardiac symptoms (personal communication, V. Frankos, Center for Food Safety and Applied Nutrition, FDA, May 30, 2007; Haller et al., in press).

Challenges in Adverse Event Data Collection Process and Analysis

Many experts and organizations have discussed challenges related to various aspects of monitoring adverse events from dietary supplements (see Kingston in Appendix B; LSRO, 2004; OIG, 2001; Woolf, 2006). For example, a 2001 report from the U.S. Department of Health and Human

Services (HHS) Office of the Inspector General (OIG) provides a detailed analysis of the effectiveness of the FDA's adverse event reporting system for dietary supplements in protecting the consumer (OIG, 2001). Although underreporting and suboptimal data quality are both attributes of a passive and voluntary system of surveillance, there are well-known advantages to a voluntary system, such as its nationwide character and the ability to distinguish at-risk groups and to generate safety signals.

This section highlights some of the challenges of the FDA's current system, many of which also apply to military reporting efforts (see below).

Data Collection Process

Low reporting rate When reported by the patient, adverse events are frequently described not directly to the FDA but to a health care provider. Receiving such information via the health care provider has obvious advantages in providing quality data, including the use of standardized medical terminology (e.g., symptoms, medications) and the opportunity to acquire additional information from the patient's medical records. Unfortunately, under the current voluntary system, the report rate is low—the OIG estimated in 2001 that less than 1 percent of all adverse events are reported to the FDA—for any of the following possible reasons. First, there is generally little consumer awareness of the importance of reporting adverse events from dietary supplements or even about the availability of a reporting system; if an individual is aware of the system, lack of familiarity with the form or lack of clarity in questions might deter submission. Second, patients are often reluctant to report the use of alternative treatments to their health care providers (IOM and NRC, 2005). Third, for some consumers, dietary supplements might be regarded as inherently safe since they are "natural," and consumers therefore fail to make a connection between use of a dietary supplement and the adverse effect, and do not report it (Ashar et al., 2008; IOM, 2005). Fourth, there is no clear common knowledge of what constitutes an adverse event (e.g., for some, only death or permanent disability would qualify, while others would include discomfort leading to absence from work, or admission to an emergency room for treatment of a symptom such as dehydration). Finally, recording the dietary history or asking about dietary supplement use is not a routine part of the medical history in either emergency room or follow-up ambulatory visits (except for ambulatory visits with some registered dietitians). While health care providers should, in theory, be sensitive to the importance of adverse event reporting, surveys have shown that even in the case of medications, physicians' beliefs and attitudes about the value of reporting adverse events contribute to low reporting rates (Figueiras et al., 1999). Other factors that might indirectly affect the report rate are the recency of introduction of the dietary supplement, media attention, and the level of educational or regulatory activity recently presented.

Quality of data collected The quality of information reported by phone or MedWatch 3500 form depends on the reporter's bias or beliefs as well as familiarity with medical reporting, signs, and symptoms. Forms filled by consumers often include incomplete or inaccurate information regarding an adverse event. For example, few consumers will be aware of how to code adverse events using standard codes for data entry (i.e., as found in the online Medical Dictionary for Regulatory Activities, which provides the coding of standard medical terminology [signs, symptoms, diagnosis, syndromes, laboratory and physiological data related to medical conditions] used by the FDA and others). To add to this difficulty, FDA safety officers do not typically probe for additional relevant information (e.g., brand name, dose, and other products or medications being taken concomitantly), nor is there much follow-up with the initial reporter to obtain more information (personal communication, V. Frankos, Center for Food Safety and Applied Nutrition, FDA, May 30, 2007).

The analysis of data from reports of adverse events related to dietary supplements is complicated by numerous unknowns about the product ingested, including the following: (1) potential product adulteration, (2) lack of identification of the part of the plant (e.g., root, seed) from which the botanical product is derived, (3) broad variation in plant nomenclature and geographical origin of plant, (4) unknown product composition due to lack of manufacturing and labeling requirements and continual product reformulation, and (5) patients' inability to accurately recall the types or number of dietary supplements being taken. The establishment of an association of an adverse event with a dietary supplement then becomes a significant challenge. An additional obstruction to data analysis is uncertainty of the duration of use or length of time between the exposure and the adverse effect.

The 2001 OIG report highlighted the difficulties presented by poor data quality. Adverse event report data were categorized as suboptimal, specifically providing limited medical information, limited information on products and manufacturers, limited information about the consumer, and limited ability to analyze trends. The report found that in 1999, the FDA recorded only 400 adverse events from dietary supplements via submission of MedWatch 3500 forms. Of those, medical records were unavailable in 58 percent of the cases, ingredients could not be determined in 32 percent, and there was no patient follow-up information available for 27 percent (OIG, 2001). The user guidance recently issued on how to fill in the MedWatch 3500 form may help those reporting adverse events to submit accurate, appropriate information.

Data Analysis: Generating Signals

Data mining is defined as the analysis of observational data sets to find unsuspected relationships and to summarize the data in novel ways that are both understandable and useful to the data user (Hand et al., 2001). Different forms of data mining can be used when the data sets are large, as in the case of adverse-event reports for medications.

The methods commonly used in pharmacovigilance to identify associations account for the variability typically found with small report counts. Quantitative evaluation can be derived from the relationships between the frequency of use of a substance and events reported, taking into consideration also all other substances' concomitant use and events (Almenoff et al., 2005). When evaluating these data, a typical challenge derives from a lack of data for the "denominator" (i.e., number of users for each dietary supplement) and low "numerator" data (i.e., number of adverse events reported for a particular dietary supplement). Data on dietary supplement sales and use (e.g., from commercial vendors or surveys) are valuable when estimating the percentage of the population that uses a dietary supplement. Signals detected by measuring disproportionality of drug-event combinations compared to known ratios from premarket efficacy trials are only statistical indicators of possible safety issues. Rare events (e.g., birth defects) are easiest to detect, but events that are commonly experienced by the population (e.g., diarrhea) are difficult to associate with the consumption of a specific dietary supplement or dietary supplement ingredient. The topic of data analysis and mining from adverse event reports is complex and has been extensively reviewed by others (Almenoff et al., 2005; Strom, 2005). Unfortunately, for the reasons described above, the quantity and quality of data reported from dietary supplement-related events is often less than desirable, resulting in weak signals for safety concerns. If higher reporting rates accompany the increase in use, awareness, and new legal requirements to report adverse events, then data mining tools might be more useful in the future.

In the case of medications, suggested signals derived from adverse event reports are complemented by other available information on the safety of the substance, such as adverse events described in clinical studies, case reports, or cohort studies (Strom, 2005). Because there is no premarket approval requirement to conduct a safety assessment for dietary supplements, manufacturers might not perform these studies, and safety data on health effects from products or interactions with other supplements or with other bioactive substances are mostly lacking. Still, both the published literature and studies sponsored by the National Center for Complementary and Alternative Medicine of the National Institutes of Health (NIH) can be used to support the attribution of adverse events to use of a particular dietary supplement. It is also encouraging that an increasing number of reports describe events from drug–dietary supplement interactions, although many are from case studies and not clinical trials.

With these serious limitations in the data quality and quantity and with reviews often conducted on a case-by-case basis, the extensive experience and appropriate expertise of the reviewers become critical when identifying signals.

THE MILITARY'S SYSTEM TO MONITOR ADVERSE EVENTS

The monitoring of adverse events related to dietary supplement use as a signal detection system within the military is integral to maintaining the health and optimal performance of military personnel. This monitoring system would be a key component of the framework recommended in Chapter 5 and would serve as a criterion to initiate reviews of research and provide important input to military commanders' policy decisions, as described in Chapter 5. It is especially important that such a system be operational at installations where military personnel face extraordinary physical and mental challenges. The military has a system to monitor adverse events from medications but does not currently have a separate and distinct system to monitor adverse events from dietary supplements. Many of the elements needed to implement such a system are already in place. The U.S. Army Medical Command has the official responsibility to make decisions regarding nutrition for all military services and would most likely address dietary supplement use and surveillance as part of that responsibility. This committee commends the military for their initiative in seeking methods to manage the safe use of dietary supplements by the troops; that is, conducting specific surveys of dietary supplement use as well as implementing educational programs and policies. The committee also acknowledges the value of past cooperation between the military and the FDA in evaluating adverse event reports from military installations at the time of high concern over ephedra use. This section describes and recommends improvements to the military adverse event monitoring system. It also describes ongoing educational efforts in the military.

Military Adverse Event Monitoring System for Medications

Each military service has established a system to collect and evaluate data on adverse events related to medication usage. Reports of adverse events are received and evaluated at the local medical treatment facility (MTF). In addition, summary reports are aggregrated and reviewed by the medical headquarters of each service as well as by the Office of the Assistant Secretary of Defense (Health Affairs). In some cases, data are also evaluated at the major command level within each service (e.g., Air Mobility Command, U.S. Army Special Operations Command, or Military Sealift Command).

All adverse events potentially associated with the use of medications by Army personnel are reported using MEDMARX,[2] a subscription-based, adverse drug reaction database. Briefly, health care personnel (physician, nurse, pharmacist, or other) at an MTF report an event to the MTF pharmacy; it would then be entered into a MEDMARX Adverse Drug Reaction (ADR) Data Entry Form (see Appendix E) by the patient safety manager or other designated person at the pharmacy. The ADR form allows MEDMARX subscribers to collect and analyze reports of adverse drug reactions. The ADR module collects information that describes the adverse reaction, the body system involved, the seriousness of the event, and the result of the reaction on level of patient care; the form also includes the Naranjo Probability Assessment Scale to determine the likelihood that use of a specific substance resulted in the adverse reaction. Adverse event reports might also be submitted via the Vaccine Adverse Event Reporting System (of the Centers for Disease Control and Prevention and the FDA) form or MedWatch 3500 form (Appendix E).

The Pharmacy and Therapeutics (P&T) Committee at each MTF—composed of physicians, nurses, pharmacists, and logisticians—is an advisory group on all matters relating to the acquisition and use of medications in an MTF. These include review of policies, review of medication errors, evaluation of clinical data on new drugs and preparations requested for use in the MTF, maintenance of the formulary of authorized medications for the installation, and review of drug adverse event reports. The P&T Committee also proposes policy decisions to the medical commander (see Hoerner in Appendix B), from medication selection to restricting availability or issuing warnings and framing educational activities. It would appear sensible for the P&T Committee in each MTF to oversee the dietary supplement functions related to adverse-event monitoring at the local level.

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[2] A national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. It facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events. It allows subscribing facilities to learn valuable lessons from the experiences of other users. Subscribers can access data from a national database of more than 1.1 million adverse drug event records. The data within MEDMARX follow standardized definitions.

Military Policies on Reporting of Adverse Events and Use of Dietary Supplements

Regulations

A review of the military policies currently in place for dietary supplements revealed that they are limited. It has been the policy of the Army Surgeon General to follow the FDA's guidance and regulations concerning such products. For example, in 2005, when the FDA announced a crackdown on products containing androstenedione (commonly known as "andro"), its possession without a prescription became a Class II felony. Possession of the substance by a service member was therefore subject to action under the Uniform Code of Military Justice.

In its Nuclear Weapons Personnel Reliability Program Regulation (DoD, 1995), the Department of Defense (DoD) establishes requirements and procedures for the implementation of the program to ensure that only the most reliable people perform duties associated with nuclear weapons. Although there is mention of prohibition of the use of alcohol and certain drugs under this program for safety reasons, there is no mention of restricting the use of dietary supplements. Likewise, there is no reference to the use of dietary supplements or reporting of adverse events included in medical requirements for Army aviation personnel (DoA, 2007).

In 2000, the Army's Office of the Surgeon General implemented policy specific to dietary supplements with a memorandum directing health care providers to document in the patient's medical record adverse events believed to be associated with dietary supplements. Health care providers should also notify the local MTF P&T Committees of any such adverse event (DoA, 2000). The memorandum also directed health care providers to report adverse events to the FDA using the MedWatch 3500 form. In addition, per the 2007 Heat Injury Prevention Policy Memorandum from the Army's Office of the Surgeon General, all cases of heat exhaustion and heatstroke reported to the Army Medical Surveillance Activity through the Reportable Medical Events System should include any history of dietary supplement use within the previous 2 weeks (USARIEM, 2007). In contrast, while heat injuries are reportable events for all services, neither the Navy nor the Air Force requires dietary supplement use to be reported (personal communication, Asha Riegodedios, Navy Environment Health Center, October 26, 2007).

There are other entities whose personnel undertake tasks with high risks and demands (e.g., Coast Guard personnel or airline pilots), and their policies to restrict the accessibility and use of dietary supplements are presented here. Recognizing the potential risks associated with dietary supplements, the U.S. Coast Guard, a branch of the Department of Homeland Security, has recently implemented regulations to manage the use of dietary supplements. They include not only specifications of the kinds of dietary supplements that may be used by all active duty members and aviators (U.S. Coast Guard, 2003), but also provisions for the submission of all reports of patient adverse reactions associated with dietary supplement use (U.S. Coast Guard, 2007). According to Coast Guard regulations, clinics shall submit all pertinent patient adverse reactions or product quality problems to the Commandant and the Maintenance and Logistics Command, using the MedWatch 3500 form. Coast Guard pharmacies are not allowed to dispense any product not approved by the FDA (i.e., any herbal supplement or other dietary supplement), with the exception of vitamins having an established Recommended Dietary Allowance. The Federal Aviation Administration, responsible for the safety of civil aviation, does not have any regulations or policy guidance concerning the use of vitamins or dietary supplements per se, except for a restriction on the use of melatonin (i.e., its use is prohibited within 12 hours of flight duty). The Air Line Pilots Association advises pilots to avoid dietary supplements that are banned by the FDA or purchased overseas (personal communication, Bill Edmunds, Air Line Pilots Association, January 25, 2008).

Education

Efforts to educate service members on the safety of specific dietary supplements include brochures and websites (Evans U.S. Army Community Hospital, 2006; Hooah 4 Health, 2007; NEHC, 2004; USACHPPM, 2000, 2003). The Navy and Marine Corps Public Health Center website provides, as part of their ShipShape weight management program, information on dietary supplements and links to the NIH Office of Dietary Supplements (ODS) website (Navy and Marine Corps Public Health Center, 2007). The ODS website offers information on dietary supplements for both the general public and scientists. The Air Force provides online information through the Human Performance Training Team website on its Air Force Knowledge Now portal. The Army offers information on dietary supplements on the Army Knowledge Online portal as part of its Ultimate Warrior Hooah Bodies and Weigh to Stay sites.

However, there is currently no centralized educational program that is effectively and consistently applied across military services and that considers specific military needs. One promising educational tool currently under development is a joint, online community of health care providers and active duty military personnel (see Jaghab in Appendix B; USACHPPM, 2007). This interactive website provides information about general nutrition, weight maintenance, and behavior management, and could be used as a centralized educational system to provide information about dietary supplements.

The importance of educating health care providers about dietary supplements was indicated by results from a 2002 survey of Army Medical Department health care providers conducted by the DoD Nutrition Committee in partnership with the U.S. Army Center for Health Promotion and Preventive Medicine, in which health care providers asked to be provided with professional development regarding dietary supplements (Corum, 2004). The Aerospace Medicine program for physicians training to become flight surgeons includes specific information on dietary supplements and active ingredients of safety concern in their online preparation materials for the Aerospace Medicine Primary course. However, it does not mention how to report adverse events involving dietary supplements, nor does the curriculum include any additional formal training on dietary supplements during the residency phase (Air Force Medical Service, 2007).

Physical trainers in military fitness centers or assigned to organizational units are also key sources of information on nutrition and health. Moreover, the more casual environment and camaraderie experienced at fitness centers may encourage openness about sharing and requesting information about nutrition needs for optimal performance, health concerns, and even adverse events experienced.

Adverse Event Data Collection Process and Analysis: Challenges and Opportunities Unique to the Military

In addition to the complications highlighted above that are commonly encountered in monitoring adverse events within the general population, the military faces unique challenges related to the activities of service members and the locations, culture, and settings in which they operate. Challenges and opportunities discussed below relate to the collection of data and analysis by using the electronic health records system.

Data Collection Process

Low reporting rate in the military Factors contributing to a low reporting rate in the general civilian population are also encountered by the military: inconsistent definitions of the term *adverse event*, a voluntary monitoring system, poor communication with health care providers (e.g., reluctance to report dietary supplement use and adverse events as well as lack of discussions about dietary supplement use during medical visits), little consumer awareness of their potential harmful effects, belief that the federal government regulates dietary supplements in the same manner as medications, and a perception that dietary supplements are inherently safe.

Other factors also affect the reporting level in the military. For example, there is no separate system to report adverse events associated with dietary supplements. The extent to which military health care providers are following the few existing military policies on dietary supplement use is also not known. Despite policies and educational efforts mentioned in the section above, recent surveys of military personnel presented to this committee indicate that a low percentage of respondents (33 percent of men and 53 percent of women among those confirming use of dietary supplements during the previous 12 months) discuss the use of dietary supplements with their health care providers (see Marriott et al. in Appendix B). Likewise, a 2002 survey conducted by the DoD Nutrition Committee in partnership with the U.S. Army Center for Health Promotion and Preventive Medicine found that only about 60 percent of primary health care providers ask their patients about dietary supplement use (Corum, 2004). Data suggest that the military reporting rate may be lower than that in the civilian population, as shown in a survey about reporting smallpox vaccine adverse events, even when adjusting for differences in representation of age and gender of subjects (McMahon et al., 2007). McMahon et al. speculated that factors contributing to this finding could be related to differences in behavior (i.e., civilian population having a lower threshold for reporting adverse events), accessibility to forms, or differences in policy implementation.

Contributing to the problem of low reporting rate is the fact that those responsible for providing education about healthy and safe behaviors, such as military commanders or medical personnel, are themselves inadequately informed about the benefits and risks of consuming dietary supplements (Corum, 2004). Physical trainers at fitness centers and assigned to organizational units might also lack such information. As a result, service members are not educated about dietary supplements at the fitness center or the treatment facility. The lack of knowledge in both patient and health care provider (or physical trainer) about dietary supplements of specific interest to the military would contribute to the infrequency of reporting adverse events associated with dietary supplement use.

An already low rate of reporting within the U.S. civilian population might be further diminished within the military by the fact that commanders have access to service members' protected health information. For example, medical officers are allowed to share patients' medical information with the commanding officer without requiring specific consent, provided that service members are adequately warned that medical record information is not confidential (DoD, 2003). This practice may restrain the willingness of service members to talk freely with military health care providers about their dietary supplement use. Other factors that may contribute to a low reporting rate might be related to unique political and cultural characteristics of military service, including mobility of the troops.

Quality of data collected The causes for low data quality or gaps in data that were identified in the FDA monitoring system are also relevant to the military system: lack of familiarity with medical reporting procedures, absence of a formalized process to probe for additional information, and challenges in obtaining data on dose consumed and dietary supplement product ingredients as well as effects from simultaneous consumption of other dietary supplements or medications. In addition, adverse event data may be submitted through various methods (e.g., FDA MedWatch forms, MEDMARX form, or the Army Reportable Medical Events System); this lack of integration allows for both duplication and absence of event reports.

Electronic Health Record Limitations and Opportunities

The military has unique opportunities not only because health care for most service members is provided within a single DoD system, but also because the military is taking pioneering steps toward the development of an electronic health records system. Despite its potential to be a state-of-the-art system, the current electronic medical record-keeping system (Armed Forces Health Longitudinal Technology Application) does not include dietary supplements as part of the patient's medication profile. Their use can be missed if the health care provider is not trained to inquire about it. Only some dietary supplements (i.e., vitamins and minerals) are included in the medication formulary of an MTF; their use can then be entered into the patient's record, which allows for the possibility of establishing relationships between reported adverse events and the use of these dietary supplements.

The switch from a paper-based system to an electronic system of documenting health-related data is in progress and will result in a longitudinal, centralized health care records system that is accessible anywhere, from the battlefield to large hospitals. This system will serve as a central, integrated clinical data repository where each patient has a single record; it will allow for aggregate analysis of data, drug interaction alerts, and patient allergy notifications (Charles et al., 2004). Such a modern computerized system will improve the ability to detect and attribute adverse events. For instance, such a system might be used to create computer-generated signals as a tool for identifying (and possibly preventing) likely specific adverse events or high-risk interactions of dietary supplements with medications or other dietary supplements, as an additional strategy to detect adverse events (Gardner and Evans, 2004). For example, a physician entering a prescription medication might be alerted to the specific risks of product interaction if the patient is using a given dietary supplement. A number of vendors have developed programs that are capable of generating alerts for medication interactions, but for most dietary supplements, the knowledge base for a similar system is not yet available. Clearly, it would be advantageous, albeit time-consuming, for the military to establish place-, unit-, or mission-specific alert rules in a manner that results exclusively in alerts that are pertinent (i.e., false alerts are minimized). In summary, if a module including dietary supplements were developed and incorporated in the patient's medication profile, this improved electronic system would permit not only the analysis of an individual adverse event, but also the analysis of dietary supplement use and adverse event trends among users in military subpopulations. Strategies to automate alerting mechanisms to prompt evaluation and reporting of adverse effects might help compensate for the problem of low reporting rates.

PROPOSED ADVERSE EVENT SURVEILLANCE SYSTEM FOR DIETARY SUPPLEMENTS FOR THE MILITARY

The Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2007 mandates that dietary supplement manufacturing companies report life-threatening events to the FDA. Non-life-threatening adverse events are to be recorded by the manufacturer, and records retained for 6 years in case the FDA needs to inspect the information. This act defines the term *adverse event* very broadly as any health-related event associated with the use of a dietary supplement that is adverse.

The term *adverse event* might identify a different effect in the context of the military. That is, the success of a military operation depends on each member's optimal performance, and thus effects that might not be perceived as a serious problem in the general population (e.g., dehydration) might constitute a significant problem in the military context, depending on the unit and task. It is therefore critical that specific adverse effects that might pose harm to military performance be reported so that leadership can take appropriate actions. With this in mind, the committee has chosen to use the FDA's definitions of adverse events and serious adverse events. For the military, the distinction between them is based on the extent of decrement to either the performance or the survivability of service members, taking into consideration their tasks (both physical and mental), the environmental surroundings (e.g., high altitude, extreme temperatures), and risks (e.g., bleeding, dehydration, infection, stress). A list of conditions to help categorize adverse events as of high, moderate, low, and minimal concern is shown in Box 5-1.

The committee's reviews of selected dietary supplements show that some supplements in popular use might present health and performance problems if misused, particularly for those subpopulations facing demanding tasks. For example, *Ginkgo biloba* and garlic have anticoagulant effects that in a combat situation might result in extended bleeding, jeopardizing health and mission success. Other supplements should not be taken while performing tasks that require alertness because of their potential for sedative effects (e.g., valerian or melatonin). The use of ephedrine-like substances is also of concern because of potential harmful cardiac effects. In addition, sales data provided to the committee indicate high use of some multi-ingredient dietary supplements; the effects of ingredient interactions are mostly unknown and present concerns. Based on the heightened risks, frequency of use among military service members, the lack of consistent policies, and the absence of a military process to report adverse events, a separate system for use by the military to monitor and evaluate adverse effects from dietary supplements is warranted. This section describes the committee's recommendations to establish such a system.

Ideally, a successful surveillance system will be economical, simple to use, and easily accessible, and yield data that are accurately representative of the population (Woolf, 2006). The data should be collected efficiently and in a consistent, unbiased manner. Vital to the effectiveness of the system is a database that allows for integrated and expeditious data analysis so that dissemination of findings to key public health officials and commanders is timely. It is also critical that encouragement to report adverse events be provided by broadening educational programs and outreach activities addressing various aspects of dietary supplement use, particularly the importance of reporting adverse events.

The lower cost of a voluntary system would make it more appropriate than an active system for use within the military population, provided that rates of response are substantially increased by educational programs and outreach activities. Active surveillance should be conducted occasionally as a tool to detect or investigate signals of concern from dietary supplements at installations whose military personnel face highly demanding tasks (e.g., Rangers or Special Forces). An active system entails a regular, periodic collection of case reports from health care providers or other personnel at those military installations. To support the data, questions about adverse effects should be included in surveys of dietary supplement use administered at these sentinel installations (see Chapter 2).

The committee also emphasizes that there is much to be gained from collaboration with other groups. The regulatory environment has not always been able to keep up with the market growth of dietary supplements. There is no single system in place for surveillance of adverse events associated with dietary supplements; nongovernmental organizations, government agencies, and manufacturers have implemented new systems or adapted systems that were already in operation for other products. Any military system of surveillance should complement its data with data from other governmental agencies and industry. Clearly, there are many limitations that would impede comparisons with databases maintained by other organizations (e.g., Consumer Product Safety Commission, the FDA, the American Association of Poison Control Centers), manufacturers, and trade associations (e.g., the American Chemistry Council, Consumer Specialty Products Association) (see description of their limitations in Kingston in Appendix B). While it is not feasible to directly integrate or equate data from these various sources, it is advisable to make in-depth comparisons, taking into consideration differences and limitations of data collection. A key committee recommendation is the formation of a partnership in which various parties with common interests work together in building knowledge by sharing collected data. Appendix B includes a description of postmarket surveillance efforts by both the private and public sectors. Also described is the surveillance system for products regulated by the U.S. Environmental Protection Agency, a system that engages the manufacturer as the primary point of contact for reporting adverse events. This industry role entails a significant training component or outsourcing of the surveillance system and design of a database and collection system.

The following section describes the committee's recommendations in three different areas: (1) the collection and analysis of adverse event surveillance data, (2) sharing of adverse event surveillance data, and (3) training and outreach. To increase the reporting rate of adverse events, various strategies have been recommended: (1) the education of commanders, service members, and military health care personnel; (2) dual mechanisms for reporting adverse events, that is, one directly from service members and one from health care personnel; (3) a centralized reporting system; and (4) the establishment of a forum or coalition with other groups to share data from the general population on adverse events.

Recommendations present actions to take and identify the military organization logically responsible for implementing them. The committee did not attempt to include all the military organizations that might be involved with educational, decision-making, research, or other activities, but rather provided a broad organizational picture of the responsibilities.

Recommendations for the Collection and Analysis of Adverse Event Data

The recommendations in this section are related to the following questions: What is the process by which the military should monitor adverse events resulting from the use of dietary supplements? How would commanders get information in a timely fashion? How can reporting rates and data quality be improved?

A critical analysis of the 2002 survey by the U.S. Army Center for Health Promotion and Preventive Medicine recommends various educational tools, but also urges that reports of adverse events associated with dietary supplements be reported through the Army Reportable Medical

Events System. Regardless of the form used to report adverse events (e.g., MEDMARX, MedWatch 3500 form, Army Reportable Medical Events System's ADR, or other), the analysis and decision-making activities would be realized more efficiently by using a centralized process in which data are reported through an integrated electronic health record system as described earlier in this chapter. The following are recommendations to expand the current system to include reporting of adverse events from dietary supplements. Since collaboration will be critical to the success of an adverse-event monitoring system, other organizations may also play a contributory role in collecting or sharing information.

> **Recommendation 7: The military should use a centralized monitoring system for reporting dietary supplement adverse events (and data on use), in which data are recorded through the integrated electronic health record system already being implemented in the military.**

Improvement of the Electronic Health Records System

The military should ensure that future electronic health records adequately capture dietary supplement use and adverse event data. (As the military continues to move toward a single electronic health record for each service member, provisions will be needed to ensure entry of data on dietary supplement use and adverse events when service members receive health care from providers not located in the MTFs.) Implementation of a centralized system will have to address difficulties such as the need for additional staff time and training efforts to collect, identify, and code dietary supplements being used. In particular, the electronic system should do the following:

- Prompt the health care provider to ask the patient about dietary supplement use, safety, and benefits and to submit adverse event reports. It would also be appropriate to add a standard assessment question(s) as part of the routine office check-in, including inquiry about the patient's reasons for taking any supplements reported used.
- Create standardized reports that can be aggregated for analysis (e.g., at the MTF, or based on common mission requirements, deployment status, and branch of service). Reports would include data on frequency of use and adverse events.
- Generate automated alerts in response to significant change in usage or reports of adverse events attributed to a dietary supplement of particular interest, which would help with adverse event attribution and identification of trends. This feature could be customized for use at various

levels (e.g., at the MTF, or based on common mission requirements, deployment status, or branch of service).

- Generate automated alerts for individual patients when there is a risk of dietary supplement interaction with a medication or other treatment.

Recommendation 8: The military should designate a committee or military entity to be responsible for the oversight and coordination of dietary supplement-related activities, such as overseeing the adverse-event surveillance system and parallel educational components.

Based on the heightened risks, the frequency of use among military service members, the lack of consistent policies, the suspected associations between adverse events in the field and the use of dietary supplements, the absence of a military system to report these adverse events, and the potential consequences of the unguided use of dietary supplements for an individual's health or mission success, a military entity or committee (hereafter referred to as the designated oversight committee) should be designated to oversee, coordinate, and provide guidance related to the use of dietary supplements by military personnel. The alternative, continuing without a designated group, would perpetuate the suboptimization of the existing resources and data and continue to put military members at risk owing to a lack of science-based guidance, education, and policy. The committee recognizes that establishing a new entity might not be feasible, and the tasks of an existing military committee or entity could be expanded to include responsibilities related to dietary supplements. In addition to a key role in designing an adverse event reporting system for dietary supplements, this oversight committee should have access to military and nonmilitary information and data, and provide advice on surveillance, educational programs, adverse event reporting, and research activities (see a description of these tasks below). The actual operational and data collection activities would rest with other existing military organizations, such as U.S. Army Research Institute of Environmental Medicine (research), the Center for Health Promotion and Preventive Medicine (educational materials), or DoD's Health Affairs Office (surveillance).

This designated oversight committee should include the expertise of nutritionists, dietitians, epidemiologists, toxicologists, pharmacists, experts on adverse event reporting, physiologists, health promotion staff, health educators, physicians and health care providers, and military leadership.

One possibility to consider would be to include oversight for these activities in the formal charter of the DoD Dietary Supplement and Other Self-Care Products Committee under the authority of the Office of the Assistant Secretary of Defense (Health Affairs) (see Box 6-1), which addresses nutrition issues including those relating to dietary supplements.

BOX 6-1
Dietary Supplement and Other Self-Care Products Committee

The Dietary Supplement and Other Self-Care Products Committee (DSOPC) has requested an official charter from DoD Health Affairs. According to their draft charter, the DSOPC shall use peer-reviewed and militarily relevant research, evidence-based data, and the consensus of subject-matter experts to develop recommendations that support DoD activities, policies, and instructions relating to dietary supplements and other self-care products used to enhance health and human performance. Specifically, the DSOPC should do the following:

- Establish Memorandums of Understanding with the FDA (1) to identify, in collaboration with the FDA, adverse events and their association, when possible, with particular dietary supplements and other self-care products used by the U.S. population; (2) to monitor and evaluate records of adverse outcomes for military beneficiaries.
- Recommend methodologies for assessing prevalence of use of dietary supplements and other performance-enhancing/self-care products across and within DoD active duty populations and their family members.
- Review trends on the use of dietary supplements and other performance-enhancing/self-care products.
- Assemble and document servicewide activities relating to dietary supplement use, education, and research.
- Review servicewide educational approaches for military health care providers (physicians, nurses, dietitians, etc.) and for the active duty population regarding the benefits and hazards of dietary supplement and other self-care product use.
- Provide recommendations for and prioritize an operationally relevant research agenda on dietary supplements for health and human performance as well as other self-care products.
- Develop evidence-based recommendations, in collaboration with other agencies, for servicewide policies that provide guidance on the use of dietary supplements and other self-care products for health and human performance for active duty personnel.
- Make recommendations to the Office of the Assistant Secretary of Defense for Health Affairs regarding appropriate resourcing and resource sharing for DSOPC initiatives among the services.
- Recommend methodology for development of a DoD system-wide communication process for reporting and dissemination of all adverse events, current research initiatives, educational programs, and implementation instructions relating to dietary supplements and other self-care products.
- Serve as a consultant on the role of dietary supplements and other self-care products in human performance and health and medical conditions for unified and specified commands upon request.

SOURCE: Personal communication, Patricia Deuster, Uniformed Services University of the Health Sciences, June 22, 2007.

This committee should review on an annual basis reported adverse events as well as surveys of supplement use by military personnel and, as indicated, recommend to the military leadership immediate action and/or conducting a review of published science-based safety reviews by the review panel. The following are specific responsibilities of the designated oversight committee.

Develop adverse event submissions systems The committee recommends the development of two reporting mechanisms, one for use by the health care provider and one for use directly by the service member. The health care provider would enter dietary supplement use information in the patient's record and submit appropriate adverse event forms to the MTF P&T Committee. In addition, service members should be able to report adverse events without having to arrange a medical appointment. Adverse event report data should be submitted through a toll-free telephone number or interactive website that allows for follow-up by medical personnel. These data should be provided to the MTF P&T Committee in a timely manner to be evaluated along with other adverse events reported from health care providers.

The designated oversight committee will clearly define the systems intended to submit the adverse event reports, including the forms to be used (e.g., MedWatch, MEDMARX ADR) by health care providers and directly by service members; the committee will also designate a system to categorize adverse events by level of severity.

Participate in forum or coalition The designated oversight committee should participate in a forum or coalition of military (i.e., the DoD and the corresponding support structures within each military service) and nonmilitary groups for the exchange of data and information related to dietary supplements, including data on adverse event reports (see below).

Develop and implement reporting mechanisms For an adverse event reporting approach to be of value, it is critical to have an efficient system to provide timely information about adverse events to those who need it (e.g., MTF P&T Committees, commanders, fitness centers and unit trainers, health care providers). After adverse event report summaries are written (see below), the flow of information to share adverse event data and summaries by the various military groups should be defined (e.g., frequency of reporting and recipients of information). The designated oversight committee should establish a system of information flow that is effective (i.e., information is delivered to decision makers and educators) and timely (see Figure 6-1).

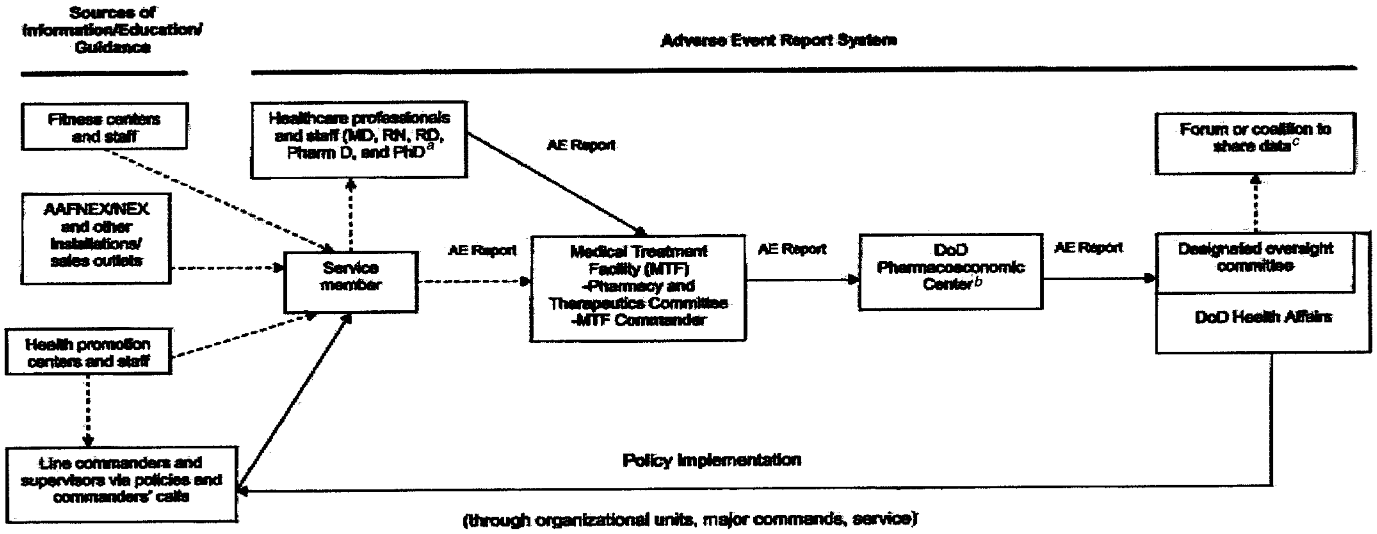
Sources of Information/Education/ Guidance
Adverse Event Report System
Fitness centers and staff
AAFNEX/NEX and other installations/ sales outlets
Health promotion centers and staff
Line commanders and supervisors via policies and commanders' calls
Healthcare professionals and staff (MD, RN, RD, Pharm D, and PhD^a
Service member
AE Report
AE Report
Medical Treatment Facility (MTF) -Pharmacy and Therapeutics Committee -MTF Commander
AE Report
DoD Pharmacoeconomic Center^b
AE Report
Forum or coalition to share data^c
Designated oversight committee
DoD Health Affairs
Policy implementation
(through organizational units, major commands, service)

FIGURE 6-1 Proposed information flow for the recommended adverse-event monitoring system.

——→ Formal Chain of Command.

- - - -→ Input, coordination, and collaboration.

[a] MD (Doctor of Medicine); RN (Registered Nurse); RD (Registered Dietitian); PharmD. (Doctor of Pharmacy); PA (Physician Assistant).

[b] Representatives from each military service, pharmacists, epidemiologists, clinicians, nutritionists, pharmacoepidemiologists.

[c] Designated oversight committee members, registered dietitians from each military service, USARIEM, pharmacist from the DoD Pharmacoeconomic Center and services, medical representative from each service, FDA's Center for Food Safety and Applied Nutrition, Federal Trade Commission, NIH's Office of Dietary Supplements, AAFEX/NEX (Army and Air Force Exchange Service/Navy Exchange Service), and other sales outlets located on military installations; industry trade association; Health and Wellness and Health Promotion Centers from the services, fitness centers or units trainers from the services.

Collect relevant data The designated oversight committee should identify relevant databases and efforts related to surveillance of adverse events associated with the use of dietary supplements by military and nonmilitary groups. The following information should be collected:

- Data on adverse events—This task is related to the designated oversight committee's participation in a partnership with other military and nonmilitary groups (see below for a list of the type of data and information to be collected).
- Information on dietary supplement product ingredients to create a database in collaboration with the FDA, the NIH's Office of Dietary Supplements, the U.S. Department of Agriculture, and the U.S. Pharmacopeia—In the future, such a database would be useful to estimate dosage and ingredients consumed and, in turn, to analyze adverse event data.
- Data on dietary supplement use and associated benefits and risks, including those from interactions with medications, other dietary supplements, or foods—of particular interest are data on risks and benefits when subjects are in environments similar to those experienced by military personnel. These data should be obtained from the expert panel conducting reviews of dietary supplements under the oversight of USARIEM (see Chapter 5).

Recommend policy The designated oversight committee should provide guidance to the DoD on military policies and regulations on the safety (and efficacy) of dietary supplement usage, such as strategies, educational programs, and materials highlighting benefits and risks of dietary supplement use for military members, as well as for health care professionals (see below).

> **Recommendation 9: The responsibility of the local Medical Treatment Facilities' Pharmacy and Therapeutics Committees should be extended to reviewing and summarizing the adverse event reports as submitted by health care providers or service members, and preparing and providing summaries via a process recommended by the designated oversight committee.**

Extension of the responsibility of the MTF's P&T Committees The military should assign specific responsibility for the oversight and coordination of the monitoring system and parallel education components at the local level. Because the local MTF P&T Committees already review adverse reactions to drugs, the committee concludes that it would be feasible to expand their responsibilities to review adverse reactions to dietary supplements at the local level. Modifications of the pertinent regulations (e.g., AFI 44-102, Medical Care Management, Paragraph 10.9) to include review and analysis of dietary supplement adverse events at the local level will ensure that local actions are initiated when appropriate. It may also be appropriate to identify the need for organizational units (e.g., Aerospace Medicine and U.S. Army Center for Health Promotion and Preventive Medicine) at the installation level to address dietary supplement usage and safety, as these organizational units have the responsibility to "optimize and enhance human performance" (e.g., AFI 40-101, *Health Promotion Program*; AFPD 48-1, *Aerospace Medical Program*; AFI 48-101, *Aerospace Medical Program*; AFI 40-104, *Nutrition Education*; AR 40-3, *Medical, Dental, and Veterinary Care*; and NAVMED P-117, *Manual of the Medical Department*).

Review of adverse events associated with dietary supplement use The committee supports the 2000 memorandum from the Army's Office of the Surgeon General (DoA, 2000) stating that adverse events believed to be associated with dietary supplements should be documented by health care providers in the patient's medical record. The committee also supports the local MTF P&T Committees' notification of any such adverse event by health care providers. The MTF P&T Committees should develop summaries of these adverse event reports highlighting dietary supplements of concern and associated adverse events, and particularly emphasizing those concerns related to military performance and environments of specific military groups (e.g., Special Forces, Rangers).

Enhance the expertise of adverse event reviewers Adverse event reviewers should include experts on epidemiology and adverse event surveillance, data mining and statistical techniques, nutrition, toxicology, diagnosis of diseases or conditions, physiology, and botany and pharmacognosy. Reviewers should be familiar with the demands and conditions unique to military operations and experienced in identifying serious or unexpected adverse effects, especially when relevant to military performance.

Submit reports on adverse events through the military system To ensure that data are available in a timely manner to military commanders and then released to the FDA as the military deems appropriate, summaries of the adverse event reports should be submitted by the MTF's P&T Committees through a designated system. The frequency and specific process to submit these summaries should be established by the designated oversight committee.

Recommendation to Share Adverse Event Data and Other Information Related to Dietary Supplements

Recommendation 10: The committee recommends that a coalition or forum be established for the exchange of data and information related to dietary supplements, such as data from surveillance of dietary supplement use and adverse events.

The committee found that only by establishing a joint forum or coalition will there be assurance that key data about reported adverse events would be shared by the FDA, military institutions, PCCs, and others. Although it is not appropriate to make direct comparisons of the data because of differences in data collection approaches, it is advisable to make in-depth examinations that take into consideration these differences and other data limitations. Members of this forum will also share other valuable information regarding new products in the market, increases in popularity of products, and latest research updates (see a list of suggested data and information to share below). With effective communication, there is much to be gained from such collaboration.

The members of this forum or coalition would update or add new data to a database established for this purpose. They could also meet periodically to present data and information updates. Members of the designated committee to oversee dietary supplement activities would participate in this coalition and have access to the database. Participants of the forum should include, among others, experts in toxicology and safety evaluation of natural products.

Representatives from the following groups could be invited to become part of this partnership:

- Designated oversight committee (recommended by this committee to come under the purview of the DoD)
- Registered dietitians from the U.S. Air Force, U.S. Army, and U.S. Navy (DoD Nutrition Committee)
- USARIEM
- Pharmacists from the DoD Pharmacoeconomic Center, U.S. Air Force, U.S. Army, and U.S. Navy
- Medical representatives from the U.S. Air Force, U.S. Army, and U.S. Navy
- FDA's Center for Food Safety and Applied Nutrition
- Federal Trade Commission (FTC)
- NIH Office of Dietary Supplements
- Army and Air Force Exchange Service/Navy Exchange Service (AAFES/NEX)

- Other sales outlets located on military installations
- Industry trade associations
- Health and Wellness and Health Promotion Centers from the U.S. Air Force, U.S. Army, and U.S. Navy
- Fitness centers or unit trainers from the U.S. Air Force, U.S. Army, and U.S. Navy
- Other representatives

To support the goal of the partnership, the collaboration might include sharing information and fostering discussion on the following topics:

- Sales outlet reports from AAFES/NEX, Defense Commissary Agency, and/or other sources at military installations to compare sales of dietary supplements from year to year and identify new products introduced to the market
- Reports from industry trade associations on changes in products and sales trends
- Summary of adverse events from specific military installations to identify regional differences, active surveillance data on adverse events at sentinel installations, and overall trends
- Summary of FDA adverse event reports as available, including relevant data from the PCCs; in addition, data on health claims of efficacy for dietary supplements would also be shared as appropriate
- Summary of FTC evaluation of dietary supplement products
- Summary of clinical trials registered by the NIH Center for Alternative Medicine evaluating dietary supplements
- Reports about dietary supplement use from in-depth surveys on sentinel installations—sentinel sites would be selected based on the mission of forces stationed at the installation (e.g., Rangers, Army Special Forces, Air Force Special Operations Command, B-1B long-range bomber crew, Navy Seals) as well as the capacity to conduct such a survey (i.e., provision of electronic health records, health care personnel to manage the additional data collection) (see Chapter 2)
- Reports from USARIEM on performance-enhancing supplements selected for review as well as a summary of research findings and protocols
- Summary of medication and dietary supplement education and materials (e.g., on safety, efficacy, interaction with medications) provided by pharmacy, health-promotion, dietetics, nursing, and medical staff to meet the requirements of the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO, 2007)
- Review of efforts by each service to provide education on dietary

supplements to their personnel (e.g., usage of websites and attendance of meetings about dietary supplements)

- Results from DoD's Survey of Health Related Behaviors that summarize trends in use and the characteristics of dietary supplement users

Recommendations to Expand Education: Training and Outreach

Recommendation 11: Military service members and commanders should be educated to recognize both the potential adverse effects and benefits from using specific dietary supplements and the importance (and the process) of reporting an adverse event.

Recommendation 12: Health care personnel should be trained in evaluating dietary supplement use, informing and obtaining information from their patients, and appropriately reporting adverse events.

The committee recommends expansion of all educational programs and outreach activities to increase awareness about the use of dietary supplements. These educational elements are key to the support of an effective, centralized adverse event monitoring system. If the evaluation of these educational activities shows that they are ineffective at improving the quality or rate of adverse event reporting from dietary supplement use, the military could explore additional strategies. For instance, in addition to continuing educational efforts, the DoD could subcontract a dietary supplement information and safety hotline service for military personnel to communicate, anonymously, with a health care specialist. This hotline service would serve two purposes, education of the service member and data collection of adverse events.

The following are recommendations for educational activities:

Develop educational materials on dietary supplements and balanced nutrition, tailored to military members The proposed designated oversight committee should oversee the development of educational materials to be disseminated through a variety of methods (e.g., posters, websites, or point-of-sale brochures). Such educational materials on dietary supplements will describe potential benefits, mechanisms of action, and how to report adverse effects. These materials should focus on the military's special performance requirements and the need to protect each individual's body and health; messages should connect the need to protect health with the importance of reporting adverse events. These messages should also emphasize that while some symptoms (e.g., diarrhea) are not particularly problematic while in garrison, they may be of concern during deployment when mission readiness becomes critical. When available or displayed at point of sale, these materials will remind and encourage the service member to contact the user's primary physician or emergency room in the event that adverse effects are experienced, even if they do not require medical intervention.

Actively pursue outreach activities Service members and their commanders must be educated so that they recognize both the potential adverse effects and the benefits from the use of a given dietary supplement, and the importance of reporting any adverse events to health care providers. This may be achieved through the following approaches:

- Include information about dietary supplements in routine commanders' calls and communication regarding force protection/performance enhancement and health promotion, to reinforce the concept that some dietary supplements should be used with care and the importance for force protection of reporting adverse effects. Military commanders will be made aware of issues surrounding dietary supplement use as part of their formal education and routinely rely on their medical staff for input. There will also be direct communication with the designated oversight committee or via summary tables and monographs, produced by the review panel, or other educational materials that are provided both to medical staff and commanders.
- Consider modifying current contracts for sale of dietary supplements to include requirements to allow placement of outreach and educational materials about dietary supplements at point of sale on military installations (e.g., AAFES/NEX outlets and fitness centers).

Provide appropriate training and continuing education for health care personnel Health care personnel (e.g., emergency room staff, flight surgeons, medics, dietitians, pharmacists, and health promotion personnel) should improve their abilities to evaluate dietary supplement use, to inform military members, and to appropriately report adverse events. Education should be included in existing programs (e.g., Uniformed Services University of Health Sciences, internships and residencies, aerospace medicine training, independent duty medical technician training, and mandatory continuing education at medical staff meetings).

Education and training should emphasize the following objectives:

- Enhance health care personnel's awareness of and ability to pose relevant questions and provide information to patients about the use of dietary supplements. Identify and direct their patients to credible sources of information (e.g., NIH Office of Dietary Supplements).
- Provide guidelines on how to effectively report adverse events. Training should address the following topics: (1) identification of adverse

events of interest to the military (see Box 5-1), (2) the forms and process used to report adverse events, (3) effective collection of the data necessary to evaluate an adverse event (e.g., include listing of different names by which the dietary supplement is known; prompt patient on whether the product information was confirmed from product label or website, whether product was taken in accordance with instructions on the product label, and to identify any other medications, dietary supplements, or foods consumed; verify contact information for follow-up), and (4) actions likely to be considered based on adverse event monitoring reports.

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7

Research Needs

The committee was requested to select a limited number of dietary supplements to review and then determine whether further examination and integrative evaluation or research on each is warranted. There are numerous research questions about the safety and efficacy of the selected dietary supplements. A first step in developing a research agenda, however, is to set priorities to deliver answers to the questions most critical to the military with the most efficient use of resources. In a complex institution like the military, whose subpopulations within the various services might have different tasks, the coordination of efforts to prioritize research needs is key to the success of this endeavor. Consequently, the committee did not attempt to provide an exhaustive listing of research needs for any dietary supplement; instead, the committee presents an approach for the military to use to prioritize research needs. For example, research might focus on supplements with anticoagulant effects as a potential critical concern, regardless of the potential benefit for which they are marketed. Box 7-1 lists examples of research needs for the supplements reviewed in this report.

Future studies on dietary supplement use in the military should be approached from an etiological or mechanistic perspective, focusing on areas of particular concern or potential benefit for health, performance, and survivability (e.g., fitness level, hydration; gastrointestinal tract, hepatic, and cardiovascular function; and cognitive and neurobehavioral function). In agreement with the committee's recommendation that both risks and benefits be considered in management decisions about dietary supplements, studies that focus on answering questions about potential safety concerns and putative benefits may need to be prioritized separately according to the

BOX 7-1
Examples of Potential Research Questions on the Dietary Supplements Selected for Committee Evaluation

Of the supplements selected for review, the committee found no compelling reason for the military to make research on the following dietary supplements a high priority at this time: chromium, dehydroepiandrosterone, garlic, ephedra, ginseng, melatonin, valerian, and *Ginkgo biloba*. For the remaining dietary supplements reviewed by the committee, further investigation into the following specific questions may be warranted:

- What is the range of consumption of caffeine in the military population? What are the sources and amounts of total intake? To what extent are patterns of consumption approaching the limits for operationally effective doses of caffeine?
- What are the beneficial or adverse effects of long-term use of tyrosine? Of creatine?
- Are there tolerance or withdrawal effects from using creatine, caffeine, or other dietary supplements?
- Given that β-Hydroxy-β-methylbutyrate (HMB) appears to improve muscle function or mass in physically untrained subjects or those in a catabolic state, what are the effects of HMB in new recruits or those with hypocaloric intake?
- What are the effects of varying the protein content (amount and composition of amino acids) in sports bars or drinks and the timing of their consumption on recovery from strenuous activity (e.g., on reduction of immune suppression after exercise, hydration, or reduction of muscle soreness)?
- Are there any dietary supplements (e.g., quercetin) that help reduce post-stress health effects such as respiratory infections?

special needs of military subpopulations. The military has unusual access to its members' medical records, and its population is in better general health and includes fewer individuals at risk for certain diseases and drug interactions, all of which should facilitate the identification of potential concerns and possible benefits associated with the use of dietary supplements by service members.

KEY CONSIDERATIONS FOR CONDUCTING MILITARY NUTRITION RESEARCH

Study Designs

In conducting research of interest to the military, it is critical that the efficacy and safety of dietary supplements be tested with representative subjects engaged in training that is similar to combat and in specific military conditions (e.g., in situations of sleep deprivation, extreme environments, moderate physical activity of long duration). Study designs should continue to include human models that mimic some of the physical stresses and environments that accompany military missions and training programs. For example, a human model could consist of individuals exercising on a predefined, outdoor running and obstacle course or a specific physical activity in an environmentally controlled laboratory setting.

The selection of study subjects should take into consideration physiological differences (e.g., blood pressure, body mass index) that reflect demographic factors (i.e., gender, age, or ethnicities) of the military population that might result in differential effects of dietary supplements. Research populations should represent the current targeted population participating in garrison training, serving in combat, or both.

Animal Models

Although the military can conduct studies of the effects of dietary supplements on subjects undergoing the physical stresses of training or conditions simulating combat, using human models for the simulation of severe mental and emotional stress presents practical and ethical limitations. Likewise, some procedures (e.g., multiple liver biopsies) would be difficult to justify on humans. The military should therefore continue the development of animal model systems that mimic the stresses of garrison training and combat to allow screening for the physiological effects of dietary supplements under extreme conditions. Screening with well-designed and ethical animal studies could be followed with more focused and better-designed human studies. These models would not only provide preliminary information about the effects of dietary supplements but could also be applied to obtaining preliminary information about the effects of other interventions in preventing and treating diseases and injuries under conditions of garrison training and combat. To maximize and coordinate efforts in this area, collaboration with civilian researchers is of vital importance. The following paragraphs describe key elements of an animal model research program.

Animal–Human Transposition

This committee recommends that the military support and conduct experiments to understand animal–human transpositions. It is increasingly apparent that it is not possible to directly extrapolate data obtained in animal studies to humans (IOM, 2006; NRC, 2005, 2007). Not only are there differences in biological regulation between species, but the premises for most safety studies might also be inappropriate. For example, feeding test animals with multiples of expected exposure levels to increase the sensitivity of a test may yield inaccurate results as substances may act metabolically quite differently at low levels than they do at high levels. The development of animal models allowing animal–human transposition will require better understanding of fundamental biology. For example, better understanding of the molecular and genetic regulatory bases of physiological responses to extreme environments will permit more credible qualitative and quantitative comparisons of animal and human outcomes, and hence more precise predictions of adverse effects in humans.

Methods to Quantify Stress

There are many stressors experienced by deployed service members and the corresponding stress responses can be perceived in the short or long term. Stress frequently results from military situations that include thermoregulatory challenges, physical exertion, inadequate sleep and rest, and psychological stressors such as confronting unknown, high-risk situations and the threat of death. Because of the multidimensional nature of stress, its measurement will continue to be difficult. The military should support or conduct studies on improving the methods to quantify stress.

APPROACHES TO IDENTIFYING AND SELECTING RESEARCH NEEDS

Coordinating Efforts Among Military Services

To identify dietary supplement research topics of interest to the military, a clear coordinating process needs to be implemented between all services. Ideally, this process will include input from all the services and will evaluate the potential topics as well as the feasibility and implementation of the research methods.

The highest-priority research should be performed or sponsored by the military and should occur in conjunction with monitoring the results of research conducted in the civilian population for potential military implications. As with other aspects of dietary supplement management, recommending research to be conducted or sponsored by the military should be a task for the designated oversight committee (see Chapter 6). Specific criteria for priorities or concerns might be set by the individual services and submitted to the Dietary Supplement Oversight Committee.

Identification of Research Needs for Specific Dietary Supplements

This committee recommends that gaps in data or information be identified based on the following elements of the recommended approach to manage dietary supplement use: (1) the results of the surveillance system evaluating the use of dietary supplements within the military (Chapter 2);

(2) gaps identified in the reviews conducted for specific dietary supplements, especially those issues relevant to military performance and survivability (Chapter 5); and (3) the occurrence of adverse events of military importance associated with the use of specific dietary supplements (Chapter 6). As the committee evaluated dietary supplements (Chapters 3 and 4) using the framework, it identified examples of potential research questions for the selected dietary supplements (Box 7-1).

Safety

Following the framework illustrated in Figure 5-1, the military should develop a list of adverse effects of particular concern for service members (e.g., interference with blood clotting). One potential response for the military would be to generate requests for proposals for methods to evaluate safety in these areas or to identify any particular classes of compounds that could be expected to cause such safety concerns.

Benefit

There is a long history of use of botanicals (e.g., Chinese traditional medicines) with putative beneficial effects that could be the subject of research by the military. The committee recommends that the military narrow its research questions to those traditional botanicals that are believed to affect physical and mental functions; one approach to focus their searches might be consultation with expert ethnobotanists and pharmacognocists.

In addition, the military should consider conducting research to develop a framework approach to determine the efficacy of dietary supplements. Such an approach should consist of a mechanism to determine the level of benefit to service members under specific environmental conditions and for specific military tasks; it should include elements such as recommendations for appropriate research designs, for conducting literature reviews, and for identifying research gaps.

Concomitantly, the military could take a similar approach as that suggested for safety, that is, to make requests for proposals that address methods for evaluation of efficacy, any particular class of compound that might be expected to confer these benefits, or both.

POTENTIAL RESEARCH AREAS OF INTEREST

Research on Adverse Effects from Supplements Relevant to the Military

As mentioned above, the military should determine the adverse effects of dietary supplements in the context of specific military environments and tasks. Broad research areas that would shed light on the safety of dietary supplements are described below. As with benefits, for all areas of research described, it is necessary to determine the dosage and duration of use of the dietary supplement leading to adverse effects and to consider the impact of unique military environments on these effects.

Frequency and Severity of Adverse Events

Before prioritizing research on adverse effects or taking management action, it is important to determine the frequency and severity of adverse events of interest to the military; one way to acquire this information is the use of well-designed surveys (Chapter 2). Another approach recommended by the committee is the implementation of an adverse-event monitoring system for the military (Chapter 6).

Identification of Ingredients Associated with Adverse Events

The concomitant analytical evaluation of the identity and integrity of the supplement products associated with reported adverse events is a key element in managing the use of dietary supplements. One potential strategy to conduct these analyses would be to contract with appropriate research facilities that are equipped for and experienced in chemical analysis of natural products.

Interactions with Other Compounds

When designing surveys and studies and interpreting their results, researchers should be mindful of the large number of dietary supplements available, which are often consumed in combination and whose composition is often changed or is unknown. Intake of multiple supplements could lead to interactions having either synergistic or antagonistic effects. Likewise, dietary supplements could interact with other food components or medications. Speculation on the impact of the interactions is possible based on mechanisms of action or other factors, but there is minimal research in this area.

Tolerance and Withdrawal Effects

Research should assess the development of tolerance and/or withdrawal effects following chronic use of those dietary supplements frequently consumed by the military (e.g., caffeine, creatine, tyrosine).

Multi-Ingredient Dietary Supplement Products

Multi-ingredient dietary supplements, which are frequently reformulated and for which safety data are limited, will continue to be available and used by military service members. It is critical to identify concerns (or potential benefits) associated with these products. Use of the framework developed by the committee is recommended to identify concerns associated with the use of multi-ingredient dietary supplements; the same criteria for initiating a review (i.e., frequency of use and adverse event reporting) should be followed. A high prevalence (or significant increase) of use indicated by the surveillance system, adverse event reports suggesting a potential for concern, or a known hazardous component in a multi-ingredient dietary supplement constitute signals calling for review and possibly management action. If literature reviews fail to reveal any safety data, then the military should consider conducting safety evaluation studies of the product or significant ingredients and potential effects of ingredient interactions (see above). The development of methodologies to evaluate multi-ingredient products, including potential interactions, is an area of reasearch that should be supported by the military.

Research on Beneficial Effects from Supplements Relevant to the Military

When prioritizing research on potentially beneficial dietary supplements, the military might consider the general topics described below. For all topics, determining the dosage and length of exposure necessary to observe benefits and the impact of the military's tasks and extreme operational environments on those effects are crucial research questions. (The reader is referred to the World Health Organization monographs, a series of four volumes published by the Traditional Medicines Programme in Geneva, Switzerland; the German E monographs; or the United States Pharmacopeia monographs.) In all cases, these putative benefits of dietary supplements need to be proven scientifically and compared to those provided by alternative compounds (drugs) currently used as the standard of care.

Mitigation of the Adverse Effects of Stressors on Service Member Performance

One important category of research is determining which dietary supplements would be useful in alleviating physiological fatigue resulting from sleep deprivation, shift work, and transmeridian travel. An existing example of military interest in these types of supplements is the addition of caffeinated chewing gum to some military rations. Aside from research assessing the effects of caffeine on fatigue, few studies have been conducted to evaluate the actions of other naturally occuring stimulants, despite their worldwide use.

Another category of research that might be addressed is the use of dietary supplements to moderate physiological responses to extreme environments, such as hypoxia and altitude sickness. Indigenous peoples in the Himalayan and Andes Mountains tolerate high altitude and cold with a hardiness for which no genetic link has been scientifically proven (Wu and Kayser, 2006). These groups use various herbs and other nutrients to maintain their strength and prevent altitude sickness, and these may be of interest to the military.

Other stressors regularly encountered by military personnel that might be mitigated by dietary supplements are dehydration, radiation from explosive sources, physiological and psychological stress, and exhaustion.

Prevention or Treatment of Injuries

In addition to promoting recovery from the previously mentioned stressors, dietary supplements might also facilitate wound healing, a process frequently encountered in a military setting. Many plants have been used worldwide for wound healing and related concerns (e.g., sunburn relief). Some in vitro and in vivo data suggest the beneficial effects of these plants; however, there are few experimental studies on their value in human populations.

Surveys on Dietary Supplement Use

Analysis of surveys to determine the pattern and extent of dietary supplement use is a critical element of a dietary supplement research agenda. This need has been amply discussed in Chapter 2. Briefly, the committee recommends continuing the collection of usage data by expanding the Department of Defense Health Related Behaviors Survey; it also recommends that more comprehensive surveys be conducted at select military sites where service members are likely to face higher risks due to the intensity of their training or exposure to extreme environments. As described in Chapter 5, adequate surveillance systems will help alert the military to potential concerns.

Validation of the Recommended Approach to Manage Dietary Supplements

Validation of the approach laid out by this committee is strongly recommended, especially for these elements of the approach: the surveillance system; the adverse event report monitoring system; and the framework for safety, including the recommendation to integrate consideration of risks and benefits as the basis for taking action. The efficacy of this overall approach will best be determined by an annual status report and a five-year review of results from the surveillance, the adverse-event report monitoring system, and the effectiveness of command recommendations to allow or restrict the use of specific supplements. The designated oversight committee should decide on a timeline and specific criteria to validate this approach as well as to review the results.

Research on Education Methods

Research should be conducted to identify the effectiveness of various methods of communication and outreach to educate service members, commanders, health care personnel, and physical training and fitness centers staff on the use of dietary supplements. Information should be obtained on the awareness of use and knowledge about supplements among military personnel, commanders, and military physicians.

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Appendix A

Workshop Agenda

Dietary Supplement Use by Military Personnel

Food and Nutrition Board, Institute of Medicine
The National Academies,
2101 Constitution Avenue, NW, Washington, DC
Lecture Room
February 12–13, 2007

February 12, 2007

1:00 **Welcome and Introductory Remarks**
M.R.C. Greenwood, Committee Chair

SESSION 1: INTRODUCTION

Moderator: John Erdman, Committee on Military Nutrition Research

1:15 **Perspectives on Committee's Task and Workshop Goals: Prospective Uses**
Andrew Young, U.S. Army Research Institute of Environmental Medicine

1:35 **Physiological Demands and Nutritional Needs of Military Personnel**
Scott Montain, U.S. Army Research Institute of Environmental Medicine

1:50 Efficacy of Dietary Supplements: Physical and Cognitive Performance
Harris Lieberman, U.S. Army Research Institute of Environmental Medicine

2:20 Discussion

3:00 Break

3:15 Health Policy Development and Implementation for Military Personnel
Lynn Pahland, Office of the Assistant Secretary of Defense (Health Affairs)

3:45 Monitoring Dietary Supplements of Military Medical Facilities
Paul Hoerner, Lt Col USAF, BSC, Department of Defense Patient Safety Center

4:15 Design of Surveys on Dietary Supplement Use: Factors to Consider
David Kaufman, Boston University

4:45 Discussion

5:30 Adjourn

February 13, 2007

SESSION 2: SURVEYS ON USE OF DIETARY SUPPLEMENTS

Moderator: Wayne Askew, Committee on Military Nutrition Research

8:00 Dietary Supplement Use in the United States Adult Population: An Analysis of the National Databases
Paula Gardiner, Harvard Medical School

8:30 Insights into Dietary Supplement Usage by U.S. Active Military Personnel
Steve French, National Marketing Institute

9:00 Beyond the DFAC (Dinning Facilities Administration Center): What Supplements Soldiers Are Taking and Why
Sonya Corum, Lt Col, U.S. Army Training and Doctrine Command

9:30 2006 Air Force Dietary Supplement Use Survey Information About Usage
Charity J. Thomasos, Lt Col MIL USAF, Eglin Hospital, Eglin Air Force Base, FL

10:00 **Break**

10:30 **Dietary Supplement Use in the Last 12 Months as Reported by Active Duty Military Personnel**
Bernadette Marriot, Abt Associates, Inc.

11:00 **Army Health Care Providers' Knowledge of Dietary Supplement Usage**
Danny Jaghab, Lt Col, U.S. Army Center for Health Promotion and Preventive Medicine

11:30 **Dietary Supplement Use in U.S. Army Personnel**
Harris Lieberman, U.S. Army Research Institute of Environmental Medicine

12:00 **Summary**
Cheryl Anderson, Johns Hopkins University

12:15 **Open Discussion**

12:45 **Lunch**

SESSION 3: FRAMEWORK FOR EVALUATING SAFETY

Moderator: Johanna Duyer, Committee on Military Nutrition Research

1:45 **What Do We Know About Safety and Adverse Effects of Dietary Supplements Commonly Used for Physical Performance and for Weight Loss?**
Mary Hardy, University of California, Los Angeles

2:15 **Dietary Supplements: An IOM Framework for Evaluating Safety**
Elizabeth Jeffery, University of Illinois

2:45 **Approaches for Postmarketing Adverse Effect Surveillance of Drugs and Biologicals**
Gerald J. Dal Pan, Office of Surveillance and Epidemiology, FDA

3:15 **Break**

3:30 **Current Approaches for Postmarketing Adverse Effect Surveillance of Foods and Dietary Supplements**
Bill Frankos, Division of Dietary Supplements Program, FDA

4:00 **Corporate Approaches to Safety and Postmarketing Adverse Effect Surveillance of Dietary Supplements**
Rick Kingston, SafetyCall International

4:30 **Summary**
Sanford Miller, University of Maryland

4:45 **Discussion**

5:30 **Adjourn**

Appendix B

Workshop Papers

The contents of Appendix B are provided on the CD in the back of the book.

Appendix C

Findings from Recent Surveys on Dietary Supplement Use by Military Personnel and the General Population

TABLE C-1 Findings from Recent Surveys on Dietary Supplement Use by Military Personnel and the General Population[a]

Reference	Demographics	Group	Questions
MILITARY PERSONNEL			
Corum, 2007	2003–2005 Mean age: 25.4 years (n=5,206) Response rate not known	Soldiers (ranks: E1–E9)	Health Promotion and Prevention Initiative, dietary supplements questionnaire "Estimate how often you use each of the following individual vitamin and mineral supplements (pills, tablets, gel caps, etc). For each supplement listed below: Step 1: Select ONE bubble in the yellow section that best describes how frequently you use a supplement. Step 2: Select ONE or MORE check boxes in the blue section to select the reasons you use that supplement."

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Vitamins/minerals: Multivitamin: 33.8% Vitamin C: 24.4% Calcium: 19.3% Iron: 14.4% Potassium: 12.1% Vitamin A: 12.5% Vitamin B_6: 11.5% **Ergogenic aids:** Sports drinks: 42.8% Sports bars: 17.3% Protein: 13.7% Ephedra-free: 10.1% **Herbal supplements:** Caffeine: 17.5% Ginseng: 6.7% Garlic: 5% Ginkgo: 3.9% Echinacea: 3.6%	**Motivation** Vitamins/minerals: Health Prevent illness Ergogenic aids: Performance enhancement Strength Herbal supplements: Prevent fatigue **Sources of information:** (n=2,241) Friends: 36% Magazines: 31.7% Internet: 22.1% Sales associates: 10.4% Doctors: <10% TV/radio/newspaper: <5% **Supplement purchase:** (n=2,241) Commissary/PX: 35.6% Nutrition/health food store on post: 25.3% Nutrition/health food store off post: 25.3% Mail order/Internet: 13.2% **Adverse effects:** (n=951) Abdominal pain, breathing difficulty, chest pain, dehydration, diarrhea, dizziness, heart attack, heat stroke, loss of consciousness, muscle cramping, nausea/vomiting, numbness in extremities, palpitations, tremors	**Conclusions:** • 16% listed dehydration as an adverse effect (concern) • Women and men tend to use different dietary supplements (DS) • Many of the DS used were associated with palpitations or anxiety, which could be due to caffeine • Perception that if something is sold in the base, it means it is safe **Limitations:** • Surveys not designed to relate adverse effects or benefits to any particular DS • Response rate not known • Results might be skewed because it was completed voluntarily • They do not have dietary pattern surveys of respondents • Adverse effects are *not* usually reported to health care providers

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
French, 2007	2005 Men and women 18 y and older (n=376) Response rate: 60%	Nationally representative group of U.S. adults "currently serving in the military, national guard, or reserve"	The Natural Marketing Institute ESP (E-screener panel) Questionnaire Index Supplement use in past 3 mo

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use: Any: 69% Multivitamin only: 23% Two or more supplements: 46% **Categories:** Protein powders: 14% Weight loss: 9% Herbal: 8% Sports nutrition: 8% Fiber: 4% Children's: 3% Homeopathic: 2% Condition specific: 2% **Specific:** Multivitamins: 57% Calcium: 13% Vitamin E: 9% Vitamin B: 8% Glucosamine/Chondroitin: 7% Creatine: 6% Fish oil: 5% Omega-3: 4% Flaxseed oil: 4% Amino acids: 4% Vitamin D: 3% Conjugated linoleic acid (CLA): 3% Lycopene: 2% Arginine: 1%	**Supplement purchase** (by age, military only): **18–29 years:** GNC: 28% Internet: 19% Nutrition/health food store: 8% Natural food market: 6% Mail order/catalog: 4% **30–44 years:** GNC: 19% Internet: 17% Natural food market: 12% Nutrition/health food store: 7% Mail order/catalog: 5% **45 years and older:** Internet: 23% GNC: 13% Nutrition/health food store: 13% Mail order/catalog: 10% Natural food market: 8%	**Conclusions:** • Supplement use increases with age (over age 45 y more likely), higher income, and higher education in military • Military more likely to use multivitamins only, significantly more sports-related supplement products • Study also gives information on overall use by gender • Study provides brand names of sports nutrition and muscle-building supplements used

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
French, 2007	2005 Men and women 18 y and older Response rate: 60%	Nationally representative group of U.S. adults (nonmilitary)	The Natural Marketing Institute ESP (E-screener panel) Questionnaire Index Supplement use in past 3 mo

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use: Any: 73% Multivitamin (only): 18% 2 or more supplements: 55% **Categories:** Protein powders: 4% Weight loss: 7% Herbal: 12% Sports nutrition: 2% Fiber: 8% Children's: 3% Homeopathic: 4% Condition specific: 3% **Specific:** Multivitamins: 58% Calcium: 26% Vitamin E: 20% Vitamin B: 14% Glucosamine/chondroitin: 11% Creatine: 1% Fish oil: 9% Omega-3: 7% Flaxseed oil: 6% Amino acids: 2% Vitamin D: 8% CLA: 1% Lycopene: 2% Arginine: 1%		**Conclusions:** • See above for general comments (French, 2007) • Supplement use increases with age • Nonmilitary significantly higher in DS use for specific supplements *except* for creatine, CLA, amino acids

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
GENERAL POPULATION			
Gardiner, 2007	2002 18–30 y (n=6,666) Response rate: 73.4%	National Health Interview Survey (NHIS) In-person interviews	NHIS "Have you ever used a multivitamin or vitamin?" "During the past 12 months, did you use natural herbs for your own health or treatment?"

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use Vitamin (ever): 63% Nonvitamin mineral: 17% **Of the 17%:** Echinacea: 47% Ginseng: 36% Gingko: 23% Garlic: 16% St. John's wort: 15% Peppermint: 15% Ginger: 11% Chamomile: 9% Kava: 9% Glucosamine: 4% Ephedra: 7% Prevalence of supplement use by physical activity level (any/nonvitamin): Sedentary: 34%/9% Moderate: 22%/19% High: 43%/23% Prescription medication users also taking nonvitamin/mineral supplement: 22%		**Conclusions:** • Nonvitamin and mineral supplement users were more likely to have high education, high physical activity, poor self-perceived health status; and be prescription medication users **Limitations:** • DS use is underrepresented because only those that responded positively to the question: "have you ever used a natural herb?" were further surveyed about use of specific DS; "natural herb" may be misleading • Only 35 herbs listed in survey; thousands are sold • Herbs have unique common names based on region or cultural background

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Gardiner, 2007	1999–2002 18–30 y (n=3,231) Response rates: 1999–2000: 82%, 2001–2002: 84%	National Health and Nutrition Examination Survey (NHANES) In-person interviews	NHANES "Have you used or taken any vitamins, minerals, or other dietary supplement in the past month?" If Yes, asked to provide dose, frequency, and duration of use and to show supplement container. If container was not available, asked for exact name.

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use: Any DS: 37% Nonvitamin/mineral: 7% **Of the 37%:** Multivitamin (any): 23% Vitamin C: 7% Vitamin E: 2% Vitamin B: 1.4% Iron: 2.1% Calcium: 2.6% **Of the 7%:** Sport: 2% Weight loss: 3% Herbs: 4% Prevalence of DS use by physical activity level (any DS/nonvitamin): Sedentary: 30%/5% Moderate: 38%/5% High: 41%/9% Prevalence of DS use among prescription medication users (any DS/nonvitamin): 45%/7%		**Conclusion:** Supplement users more likely to be ages 23–30 y female, non-Hispanic white, have high self-perceived health status, and have high physical activity level **Limitations:** • DS use likely underrepresented because survey does not include teas, loose herbs, etc., or DS without a bottle or label • Did not record reason for use or health condition associated with use • Did not ask about sports drinks, teas, or fortified foods

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Jaghab, 2007	(n=1,200) **Participation rate:** 15%	Army physicians (n=573) Ancillary (n=614) Located in: Iraq >40% Afghanistan >20% Other >9%	Electronic survey on Army Medical Department (AMEDD) Knowledge Management website

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Top 10 supplements reported to physicians/ ancillary: Creatine: 32.5%/27% Protein: 16.2%/26.2% Multivitamin and minerals: 13.4%/20.2% None: 11.9%/10.4% Weight loss: 10.5%/19.1% Metabolism boosters: 8.6%/8.8% Ephedra: 7.7%/5.2% Bodybuilders: 6.6%/7.7% Glucosamine and chondroitin: 3.5%/3.7% Nitrous oxide: 2.8%/5.7% Caffeine: 2.8% (to physicians) Herbal preparations: 3.7% (to ancillary)	**Top 5 reasons took supplements** reported to physicians/ancillary: Performance enhancer: 52.5%/48.5% Gain weight: 24.3%/22.1% Lose weight: 23.9%/27% Increase muscle mass/ conditioning/strength: 6.1%/6.5% Cognitive enhancer/stay awake: 3.7% (to physicians only) Supplement diet/health maintenance: 3.6% (to ancillary only) **Supplement purchase:** PX: 52%/59.3% Online: 35.4%/39.9% GNC: 22%/15% Given or sent: 13.1%/14.2% Unknown: 11.7%/4.9% Local markets: 2.8%/1.8%	**Educational suggestions:** • Which supplements work and don't work • Better nutrition in general • General risks of taking supplements • Weight-loss supplement education Study also provides top 5 brands of supplements used **Concerns about side effects** (from physicians and ancillary): • Interaction of supplements with medications or other supplements • Dehydration • Side effects (general) • Renal/kidney functions • Heat injury/heat stress • Supplements are not regulated by the FDA • Safety of taking supplements • Cardiac issues • Overuse of supplements • DS users don't understand the risks and complications of the supplements • Long-term effects

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Kaufman, 2007	2005 Men and women, all ages Adults (n=2,684) Children (<18 y) (n=581) (if under 14 y, parents answer) **Participation rate:** 57%	National survey Telephone interviews, random digit dialing	Slone survey "We are interested in all medicines which you have taken in the past 7 days. These include prescriptions from your doctor or clinic, nonprescription medicines, vitamins, herbs, or alternative medicines." Asked to retrieve bottle and provide information on container.

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use (most commonly used): Vitamins (any): 40% Multivitamins: 26% Herbal/natural (any): 23% Lutein: 9.4% Lycopene: 7.8% Glucosamine: 4.0% Garlic: 2.6% Chondroitin: 2.5% *Ginkgo biloba*: 1.6% Co-enzyme Q: 1.5% **Other:** Prescription medication users who take one or more herbals: 30%		Slone data used as an example of survey design age group not the same as military

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Lieberman et al., 2007	(ongoing) Men and women (n=484) Average age: 29 y Response rate: 80%	General Army	

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use at least once per week: Males: 55% Females: 70% **Top 10 supplements:** **Men:** Multivitamins: 30% Sports drink: 20% Vitamin C: 13% Protein powder: 13% Vitamin E: 6% Calcium: 6% Vitamin D: 5% Vitamin A: 5% Creatine: 5% Sport bar: 5% **Women:** Multivitamins: 28% Sports drink: 28% Calcium: 15% Folate: 13% Vitamin C: 13% Iron: 10% Vitamin B_6: 10% Vitamin D: 8% Vitamin E: 8% Protein powder: 8% **Number of different supplements used per week:** **Men:** 1–2: 30% 3–4: 12% 5+: 14% **Women:** 1–2: 35% 3–4: 18% 5+: 18%	**Top 5 reasons for supplement use:** **Men:** Health Performance Muscle strength Other Energy **Women:** Health Other Energy Performance/weight loss/not sure Endurance/strength	**Conclusions:** • All Army populations surveyed consume high levels of DS • Different Army populations have different patterns of use • Editorial comment: Scientific justification for this level of supplement use is lacking Study also provides information on supplement use by age, education, occupation; supplement knowledge; and money spent on supplements per wk

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Lieberman et al., 2007	April 1999 men (n=768) Average age: 23.6 y Response rate not known	U.S. Army Rangers	
Lieberman et al., 2007	July 2000 Men (n=152) Average age: 31.3 y Response rate not known	Special Forces	

Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
Supplement use at least once per week: 81% **Top 10 supplements:** Sports drink: 41% Multivitamins: 23% Creatine: 19% Protein/amino acids: 18% Antioxidants: 14% Herbs (ginseng, garlic, etc.): 9% Carbohydrate beverage: 7% Androstenedione: 7% Sports bar: 6% Sports gel: 3% **Number of different supplements used per week:** 1–2: 45% 3–4: 19% 5+: 15%	**Top 5 reasons for supplement use:** Energy Health Muscle strength Other Physician	General comments (see above)
Supplement use at least once per week: 65% **Top 10 supplements:** Sports drink: 36% Multivitamins: 32% Protein powder: 16% Creatine: 16% Sports bar: 15% Vitamin C: 11% Meal replacement beverage: 9% Vitamin E: 7% Antioxidants: 6% Androstenedione: 6% **Number of different supplements used per week:** 1–2: 41% 3–4: 14% 5+: 7%	**Top 5 reasons for supplement use:** Health Performance Energy Other Physician	General comments (see above)

continued

TABLE C-1 Continued

Reference	Demographics	Group	Questions
Lieberman et al., 2007	1999–2001 Men and women (n=315) Average age: 44 y Response rate not known	Army War College (mid to upper management)	

	Findings: Usage	Other Findings	Authors' Conclusions and Study Limitations
	Supplement use at least once per week: Men: 71% Women: 81% **Top 10 supplements** **Men:** Multivitamins: 39% Vitamin E: 22% Vitamin C: 17% Sports drink: 10% Antioxidants: 7% B-complex: 6% Garlic: 6% Beta-carotene: 5% *Ginkgo biloba*: 5% Calcium: 5% **Women:** Multivitamins: 52% Calcium: 32% Vitamin E: 32% Vitamin C: 29% Antioxidants: 23% Beta-carotene: 16% Magnesium: 13% Folate: 13% B-complex: 13% Vitamin B_6: 10% **Number of different supplements used per week** **Men:** 1–2: 29% 3–4: 14% 5+: 12% **Women:** 1–2: 36% 3–4: 6% 5+: 23%	**Top 5 reasons for supplement use** **Men:** Health Other Performance/energy Poor diet Physician **Women:** Health Performance/energy Other Poor diet Physician	General comments (see above)

continued